BRAIN

A JOURNAL OF NEUROLOGY

XUM

MACMILLAN AND CO., LIMITED
LONDON - BOMBAY - CALCUTTA - MADRAS
MELBOURNE
ST. MARTIN'S PRESS, INC.
103 PARK AVENUE, NEW YORK 17
THE MACMILLAN CO. OF CANADA LTD.
TORONTO

Brain

A Journal of Neurology

EDITOR

SIR RUSSELL BRAIN, Bt. D.M.

ASSISTANT EDITOR

DENIS WILLIAMS, M.D.

WITH THE HELP OF

SIR WILFRID LE GROS CLARK, D.Sc., F.R.S.
J. N. CUMINGS, M.D.
AUBREY LEWIS, M.D.
D. W. C. NORTHFIELD, F.R.C.S.
DOROTHY S. RUSSELL, M.D.
D. WHITTERIDGE, D.M., F.R.S.
O. L. ZANGWILL, M.A.

Hon. Secretary and Treasurer to the Guarantors:
S. NEVIN, M.D.

VOLUME LXXXI

MACMILLAN AND CO., LIMITED
ST. MARTIN'S STREET, LONDON

* * *

ST. MARTIN'S PRESS, INC.
103 PARK AVENUE, NEW YORK 17

1958

XUM

ARBNB BINDERY 20 55

XUM

CONTENTS

	PAGE
Visual Field Changes Following Anterior Temporal Lobectomy: Their Significance in Relation to "Meyer's Loop" of the Optic Radiation. By Murray A. Falconer and John L. Wilson	1
The Architecture of the Optic Radiation in the Temporal Lobe of Man. By J. M. Van Buren and M. Baldwin	15
Primary Tumours of the Thalamus. By Wylie McKissock and Kenneth W. E. Paine	41
The Effects of Repeated Stimuli upon EEG and Vasomotor Activity During Sleep in Man. By G. Pampiglione and Brian Ackner	64
Neurological Complications of the Reticuloses. By E. C. Hutchinson, B. J. Leonard, C. Maudsley and P. O. Yates	75
Progressive Multifocal Leuko-encephalopathy. By Karl-Eric Åström, Elliott L. Mancall and Edward P. Richardson, Jr.	93
An Evaluation of Thymectomy in Myasthenia Gravis. By John A. Simpson	112
Recurrent Polyneuropathies and their Corticosteroid Treatment. By James H. Austin	157
Tonic Seizures in Disseminated Sclerosis. By W. Matthews	193
The Blood Vessels of the Human Optic Chiasma and their Relation to those of the Hypophysis and Hypothalamus. By B. H. Dawson	207
The Groping Phenomena of the Foot. By A. Fradis and M. I. Botez	218
Centrencephalic Integrating System. By Wilder Penfield	231
Internal Hydrocephalus Caused by Parasitic Cysts. By S. Kuper, H. Mendelow, and N. S. F. Proctor	235
The Spongy Type of Diffuse Sclerosis. By M. Wolman	243
The Blood-Brain Barrier: An Experimental Study with Vital Dyes. By J. W. Millen and A. Hess	248
The Diagnosis and Treatment of Wilson's Disease. By C. G. Warnock and D. W. Neill	258
Cervical Arthropathy in Syringomyelia, Tabes Dorsalis and Diabetes. By Sir Russell Brain and Marcia Wilkinson	275
Spinal Mechanism of the Abdominal and Erector Spinæ Skin Reflexes. By E. Kugelberg and K. E. Hagbarth	290
Hippocampal Projections and Related Neural Pathways to the Mid-brain in the Cat. By Walle J. H. Nauta	319
Experimental Production of Unilateral Neglect in Monkeys. By Keasley Welch and Peter Stuteville	341
The Relationship between Cortical and Peripheral Effects of Cerebellar Stimulation in the Cat. By A. Kreindler, M. Steriade and E. Zuckerman	348
Observations on the Blood Vessels of the Spinal Cord and their Responses to Motor Activity. By J. N. Blau and Geoffrey Rushworth	354
Corticobulbar Connexions to the Pons and Lower Brain-stem in Man. An Anatomical Study. By H. G. J. M. Kuypers	364
On Certain Small Tumours Encountered in the Temporal Lobe. By J. B. Cavanagh	389

U OF M BINDERY JUL 20 '59

XUM

CONTENTS

	PAGE
Effects of Temporal and Frontal Cortical Lesions on Auditory Discrimination in Monkeys. By Lawrence Weiskrantz and Mortimer Mishkin	406
The Prognosis in Aphasia in Relation of Cerebral Dominance and Handedness. By A. Subirana	415
The Physiological Basis of Consciousness. A Critical Review. By Sir Russell Brain	426
The Prognostic Value of the Muscle Biopsy in the "Floppy Infant." By J. Godwin Greenfield, Tillye Cornman and G. Milton Shy	461
Endogenous Hypoglycæmia. By Hugh Garland	485
Some Autonomic Concomitants of Ictal Automatism. A Study of Temporal Lobe Attacks. By J. M. Van Buren	505
Vestibulogenic Seizures. A Consideration of Vertiginous Seizures, with Particular Reference to Convulsions Produced by Stimulation of Labyrinthine Receptors. By Simon Behrman and Barry D. Wyke	529
Torulosis of the Central Nervous System in Britain. By F. Clifford Rose, Helen C. Grant and A. L. Jeanes	542
On Familial Ataxia, Neural Amyotrophy, and their Association with Progressive External Ophthalmoplegia. By James Stephens, Mary L. Hoover and John Denst	556
Dorsal Spinal Root Afferents to Clarke's Column. By Gunnar Grant and Bror Rexed	567
The Fasciculus Intermediolateralis of Loewenthal in Man. By Sie Pek Giok	577
The Meaning of "Postulational Psycho-physical Parallelism." By Hartwig Kuhlenbeck	588
Notices of Recent Publications	145, 268, 456, 604

XUM

MARCH 1958

BRAIN

VOL. 81, PART 1.

VISUAL FIELD CHANGES FOLLOWING ANTERIOR TEMPORAL LOBECTOMY: THEIR SIGNIFICANCE IN RELATION TO "MEYER'S LOOP" OF THE OPTIC RADIATION

BY

MURRAY A. FALCONER AND JOHN L. WILSON[1]

(From the Guy's-Maudsley Neurosurgical Unit, London)

THERE appear to be a considerable divergence of opinion as to the patterns of the visual field changes in lesions of the temporal lobe. Most authorities have based their opinions upon the field changes observed with temporal lobe tumours, and many including Cushing (1921), Kravitz (1931), Oldberg (1937), and Harrington (1939) have stressed the incongruity of the homonymous hemianopias which result from such lesions. Duke-Elder, in 1949, after surveying the extensive literature, concludes—in italics—"Lesions in the anterior parts of the (geniculocalcarine) radiations produce incongruous fields showing incomplete homonymous hemianopic defects, the asymmetry gradually decreasing in amount the farther back the lesion is situated in the visual pathway until in the occipital region the congruity of the field defects becomes absolute, extending even to minute irregularities." In a diagram (Duke-Elder, 1949, Fig. 3033) he depicts lesions of the anterior loop of the optic radiations as producing a "markedly incongruous superior quadrantopia." Earlier, Harrington (1939) had stated that "the cause of these characteristic defects is to be found, it is believed, in the dissociation in the temporal lobe of homologous fibres from corresponding retinal points and their gradual coalescence in the postparietal region."

Spalding (1952), on the other hand, in discussing the changes produced by gunshot wounds involving the visual (optic) radiations assumes that the field defects are always congruous. He illustrates how wounds of

[1]In receipt of a grant from the Medical Research Council. (Read in part at a joint meeting of the Irish Ophthalmological Society and the Society of British Neurological Surgeons in Dublin on May 18, 1957.)

XUM

the anterior temporal lobe may involve the lower margin of the anterior part of the optic radiation and produce a congruous partial upper quadrantanopia in which the horizontal meridian is spared and the field defect projects towards the fixation point in the vertical meridian. Wounds in a zone immediately behind this may involve the intermediate part of the radiation causing narrow, sector-shaped defects in the horizontal meridian reaching to the fixation point, while wounds above and behind this in the lower partial region may involve the upper margin of the radiation producing a congruous partial lower quadrantanopia.

We have, therefore, studied the visual field changes that have supervened in 50 consecutive epileptic patients treated by anterior temporal lobectomy. The findings indicate that after our particular operation, which has always opened up the anterior part of the temporal horn of the lateral ventricle, there has always been some degree of homonymous hemianopia, but that its extent has varied greatly. The hemianopia has always been congruous. In the slightest degrees it has involved only the upper portion of the contralateral fields immediately adjacent to the vertical meridian, and produced a loss so slight that it could not be detected except by the most careful quantitative perimetric studies. Then, as the visual field defects have become more severe, the loss has spread from above down in sector-shaped fashion to involve further portions of the contralateral fields. The macular region tends to be spared, except when the visual loss extends well into the lower quadrant. Two cases in our series, however, had a complete homonymous hemianopia, but with macular sparing. We have further found that with removals of less than 8 cm. there is no hard-and-fast correlation between the extent of the anterior temporal lobectomy and the severity of the resulting hemianopia, which is usually only a quadrantic defect, or less. Above a limit of 8 cm. from the temporal pole, however, the chances of a more extensive hemianopia become greater. Our findings lend support to Adolf Meyer's (1907 and 1911) views on the anatomy of the optic (geniculo-calcarine) pathways, particularly in respect of the anterior loop of the lower margin of the optic radiation around the tip of the temporal horn.

Case-material and Methods of Study

Our patients were all epileptics with intractable temporal lobe seizures submitted to unilateral anterior temporal lobectomy as outlined in a previous report (Falconer, Hill, Meyer, Mitchell, and Pond, 1955). The clinical data and therapeutic results in this particular series of 50 patients have recently been reported (Falconer, Hill, Meyer and Wilson, 1957) as have the pathological findings and their significance (Cavanagh, Falconer, and Meyer, 1957). In 18 cases the temporal lobectomy was performed in the right side, and in 32 on the left. The steps of the operation are illustrated in fig. 1, from which it can be seen that the operation has always

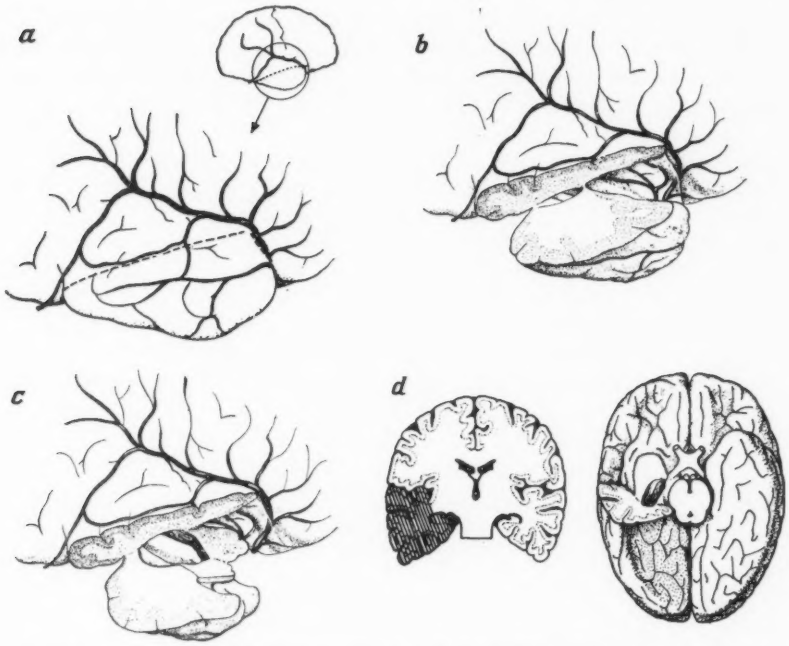


FIG. 1.—Stages of temporal lobectomy: a, first stage, showing the line of incision in relation to sylvian vessels and Labbe's vein; b, second stage, showing insula uncovered and temporal horn opened posteriorly; c, third stage, showing temporal horn opened along its roof, exposing hippocampus in its floor with choroidal plexus lying above it; d, representation of extent of removal of temporal lobe on completion of operation. (From *Lancet*, 1955, **1**, 831.)

opened into the tip of the temporal horn of the ventricle, removing the anterior portion of the hippocampus (Ammon's horn) from its floor as well as other mesial structures such as the uncus and the amygdala. The extent of the operation was always measured from the temporal pole to the point where the incision crossed the infero-lateral border of the temporal lobe and this measurement ranged between 4·5 and 9 cm. Unfortunately the extent to which the lateral wall of the temporal horn was opened from its tip was not always recorded, but in general it was roughly proportional to the amount of temporal lobe removed, and ranged between 1·5 and 3 cm. Had it been consistently recorded it might have provided a more significant figure for our purposes, because it is more directly related to the periventricular course of Meyer's anterior loop.

44 of the 50 patients were examined both before and after operation by quantitative perimetry on the Bjerrum screen and the perimeter according

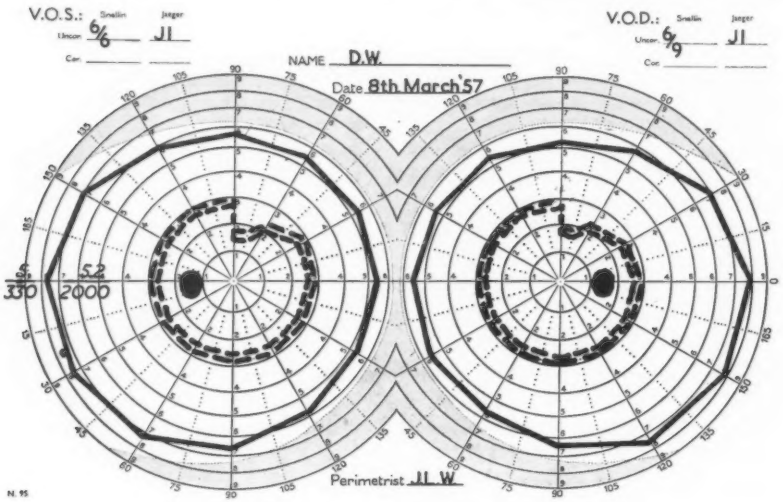
XUM

to the principles set forth by Walker (1917), by Traquair (1938), and by Hughes (1954), while the remaining 6 (all with appreciable defects) were tested by careful confrontation methods alone. These examinations were carried out by a succession of trained assistants, and in general the defects found approximately a month after operation have remained constant when retested on subsequent occasions. In a few instances, however, the post-operative visual fields were at first regarded as normal, for it was not until later that we realized it was necessary to test the upper parts of the visual fields on the Bjerrum screen at 15 degree intervals or less, and not just at the customary 30 degree intervals. Since then all such patients have been re-examined and all have been found to exhibit a minimal degree of hemianopia, not appreciable by confrontation testing. 44 of the original 50 patients have had their visual fields re-checked on the Bjerrum screen and perimeter by one of us (J. L. W.), and in 25 cases re-charted for the finer details.

Visual Field Findings

The visual field defects show every gradation from a minimal upper field loss to a complete hemianopia with, however, macular sparing. For descriptive purposes we can conveniently subdivide the degrees of hemianopia as follows:

(1) *Minimal hemianopia* (*see* figs. 2 and 3). Here there is a congruous defect involving the uppermost portion of the homonymous fields



One month following 6cm. anterior temporal lobectomy

Fig. 2.—Minimal upper homonymous hemianopia.

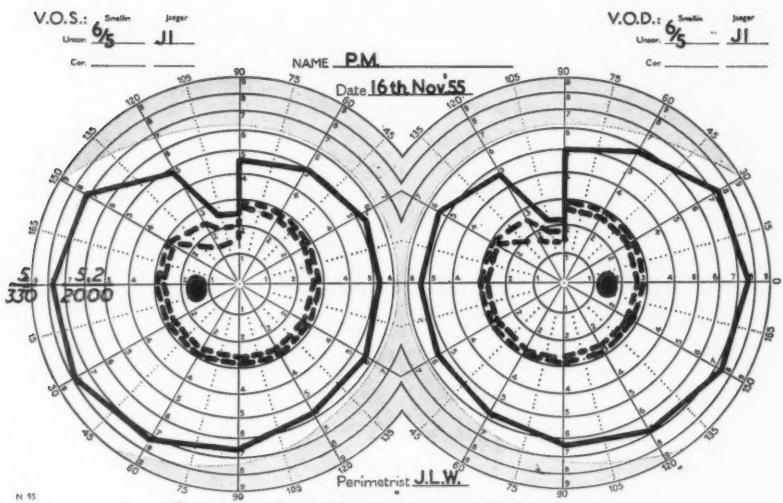


FIG. 3.—Minimal upper homonymous hemianopia.

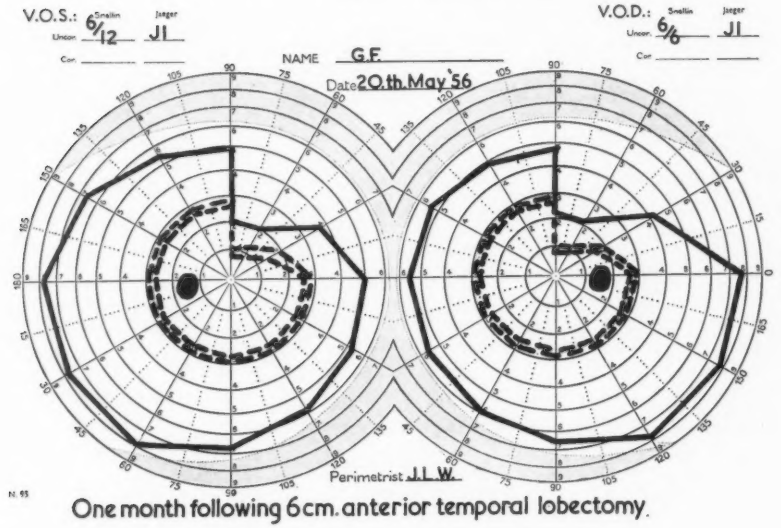


FIG. 4.—Less than a quadrantic defect.

immediately adjacent to the vertical meridian and extending laterally for only a few degrees. It may affect the isopters on both the Bjerrum screen and the perimeter, but the findings on the Bjerrum's screen are the more

sensitive (fig. 2). The edge of the defect in relation to the vertical meridian is a sharp one, but its horizontal edge is sloping. The precise delineation of these minor hemianopic defects with regard to the vertical meridian was not appreciated by earlier observers in this Unit until discovered by one of us (J. L. W.). Since then it has been confirmed by others. It strikingly resembles the visual field defect recorded by Cushing (1921) in a case of gunshot wound involving the anterior part of one temporal lobe (*see* later —fig. 9).

(2) *Less than a quadrantic defect* (*see* fig. 4). The defect fans out sectorwise from the vertical meridian, approaches towards the macula, but involves less than a quadrant.

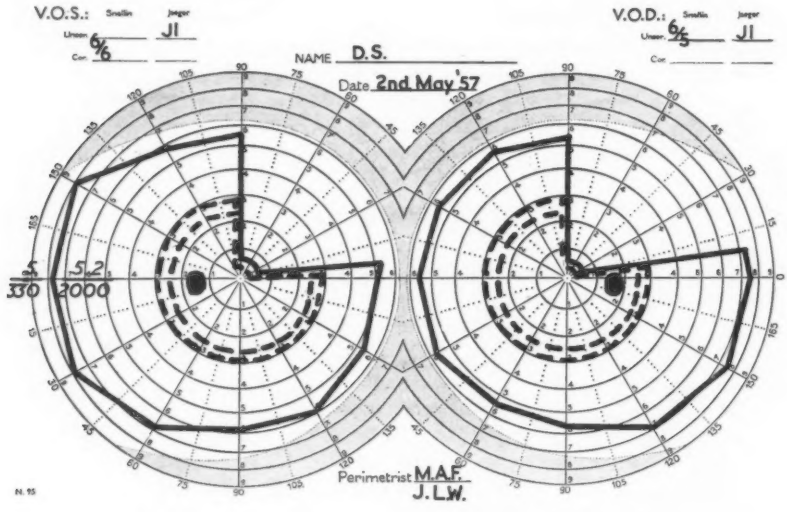


FIG. 5.—Quadrantic defect.

(3) *Quadrantic defect* (*see* fig. 5). Here the loss involves most of the upper quadrant sparing the macular region. Its edge in relation to the horizontal meridian may be sloping or sharp. At Professor Brodie Hughes' suggestion we re-examined our case-material and found that for defects, which were quadrantic or larger, the steepness of the horizontal edge might correlate with the age of the lesion. Thus, when the lesion is recent, its margin is always sloping, suggesting a lesion of the radiation, which is recovering to some degree; in other words, a mild "depressional" defect. When, however, the lesion is old, the horizontal edge is generally steep, indicating that the lesion is now static. The vertical edge of the

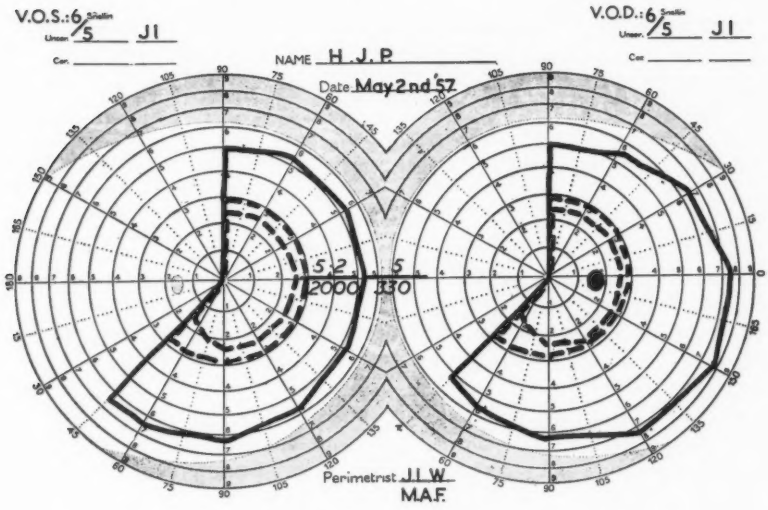


FIG. 6.—More than a quadrantic defect.

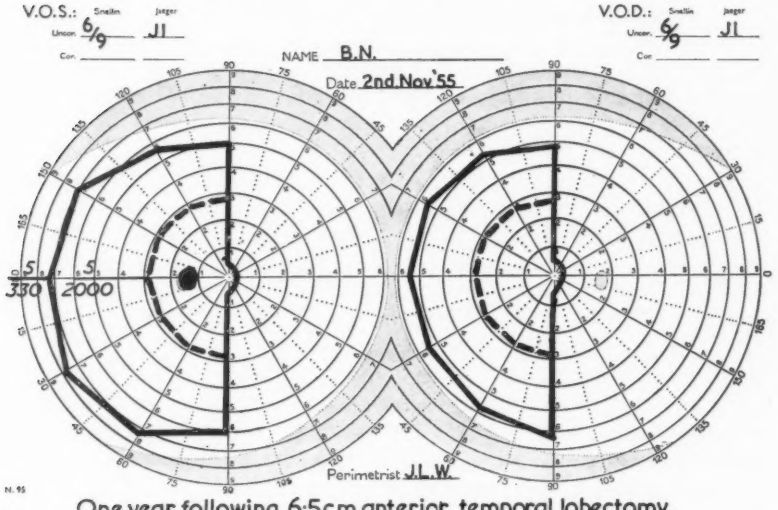


FIG. 7.—Complete homonymous hemianopia with macular sparing.

defect, coinciding as it does with the vertical meridian, is always sharp, for it represents the periphery of the homonymous field.

(4) *More than a quadrantic defect* (*see* fig. 6). Here the loss extends down below the horizontal meridian into the lower quadrant. The macular region tends to be invaded. The lower edge may be sharp or sloping.

(5) *Complete homonymous hemianopia* (*see* fig. 7). There were two examples. Both had macular sparing.

Discussion

Our findings are thus at variance with those reported by Cushing (1921), Kravitz (1931), Oldberg (1937), Harrington (1939) and others on temporal-lobe tumour material, in that our field defects were always congruous, but are in general agreement in this respect with the findings of Spalding (1952) on gunshot wounds of the temporal lobe. It is interesting to note that Traquair (1922) and Kravitz (1931) ascribed the incongruity of the visual defects with temporal-lobe tumours to pressure on the optic tract rather than to involvement of the optic radiation, while Oldberg (1937) ascribed it to pressure on the anterior choroidal artery leading to a disturbance of nutrition in the external geniculate body. We would ascribe the field defects in our particular cases to direct involvement of the optic radiation.

Penfield (1954) in his Hunterian Lecture on temporal lobe epilepsy made some general observations as to the effects of temporal lobectomy on the visual fields. He stated "When the line of removal is less than 6 cm. posterior to the tip, it is apt to result in no post-operative visual field defect. If the removal includes 6 cm. and more, it is apt to produce contralateral upper quadrantic homonymous hemianopia. When the line is pushed back to 8 cm. there is apt to be a complete homonymous hemianopic defect."

Our observations indicate that the relationship is more complex than this, and that in individual cases there is usually no hard-and-fast correlation between the amount of temporal lobe removed and the extent of the resulting homonymous hemianopia. In Table I the degrees of hemianopia following operation are compared with the extent of removal as measured from the temporal pole along the infero-lateral border of the lobe. It will be seen that even after removals of 6 cm. or less (down to 4·5 cm.) there is always some defect in the homonymous fields, although it may be minimal and not recognizable except by the most careful testing. It will also be seen that a superior quadrantanopia occurs in approximately the same proportion, viz., a half, of each of the three subgroups of excisions (4·5 to 6 cm., 6·5 to 7·5 cm., 8 to 9 cm.), while occasionally complete hemianopias can occur with removals of any degree. Of more importance, perhaps, from a practical viewpoint is the comparison made in Table II. Here the visual field losses have been divided for each of the three subgroups of excision into losses of a quadrant or less (which the patient can usually compensate for) and into losses of more than a quadrant (which

XUM

TABLE I

DEGREES OF HEMIANOPIA FOLLOWING ANTERIOR TEMPORAL LOBECTOMY

(50 Patients)

Degrees of hemianopia.	Extent of operation. 4·5-6 cm	6·5-7·5cm	8-9cm
Minimal hemianopia.	2	6	0
Less than a quadrant.	4	4	2
Quadrantic loss.	7	12	5
More than a quadrant.	1	3	2
Complete hemianopia.	1	0	1

TABLE II

COMPARISON OF HEMIANOPIA FOLLOWING ANTERIOR TEMPORAL LOBECTOMY

(50 Patients)

Severity of hemianopia.	Extent of operation. 4·5-6cm	6·5-7·5cm	8-9cm
Quadrantic or less.	13	22	7
More than a quadrant.	2	3	3
Ratio.	6·5 :1	7·3:1	2·3:1

may constitute an appreciable handicap). It will be seen that the ratio of the smaller to the larger deficit is low and approximately the same in the two subgroups of excisions of less than 8 cm. (6·5 : 1 for the subgroup

XUM

of 4·5 to 6 cm. and 7·3 : 1 for the subgroup 6·5 to 7·5 cm.) but rises to 2·3 : 1 for the subgroup of 8 to 9 cm. removals. Thus for removals of more than 8 cm., the more extensive the resection the greater are its prospects of a severe hemianopia.

There are probably several interesting factors which lead to the variations of extent of hemianopia following anterior temporal lobectomies of any given magnitude. The first is that the size of the temporal lobe proportionate to the rest of the cerebral hemisphere varied considerably, particularly in our case-material which included many cases with atrophic and sclerotic lesions originating in early childhood. Again the extent to which the optic radiation reaches forwards in the temporal lobe probably varies from patient to patient (Hughes, 1954). Yet a third factor to be considered is the likelihood of the blood supply from branches of the posterior cerebral artery to the stump of the temporal lobe having been interfered with, so producing infarctions beyond the area of excision and thereby increasing the severity of the visual field loss. We think that this factor probably operated in the two cases of complete homonymous hemianopia with macular sparing, and that posterior cerebral artery thrombosis may have occurred, for in both troublesome bleeding was encountered at operation. Certainly the field defects in these two cases are compatible with such vascular lesions (Traquair, 1938).

We may conclude therefore that for excisions of varying magnitude between 4·5 cm. and 8 cm. the pattern of the visual field defects is much the same, and resolves itself into congruous homonymous defects of usually the upper visual fields. With excisions of greater magnitude defects of similar degree may still occur, but the likelihood of the more severe defects becomes greater. This pattern of the visual field defects fits in well with the anatomical observations of Adolf Meyer (1907 and 1911) concerning the course of the fibres of the optic radiation through the temporal lobe.

Meyer arrived at his conclusions by studying the secondary degenerations which occur in the brain following old circumscribed vascular or traumatic lesions. He observed that the most ventral portion of the optic radiation, on leaving the external geniculate body, plunges forwards into the temporal lobe to sweep around the tip of the temporal horn before passing backwards at first lateral to and then beneath the ventricle to end in the calcarine cortex. He referred to this as "the peculiar detour of the ventral portion of the geniculo-calcarine path", and a diagrammatic representation of its course based on data supplied by Meyer to Cushing (1921) and later simplified by Traquair (1922) is shown in fig. 8. Others since his time have suggested that the degree of looping has been probably exaggerated in importance, and may be variable (Hughes, 1954).

Meyer did not substantiate his view by visual field studies, but he stimulated Harvey Cushing (1921) to have such studies undertaken in one

XUM

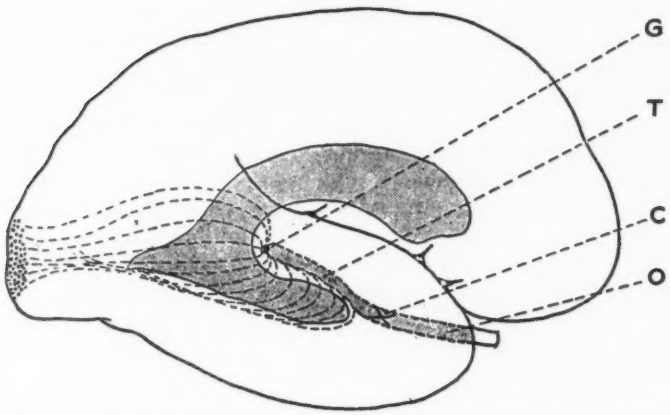


FIG. 8.—Diagrammatic representation of the geniculo-calcarine pathway according to Meyer, as modified by Cushing and by Traquair. G, geniculate body. T, optic tract. C, chiasma. D, optic nerve. (From *British Journal of Ophthalmology*, 1922, **6**, 252.)

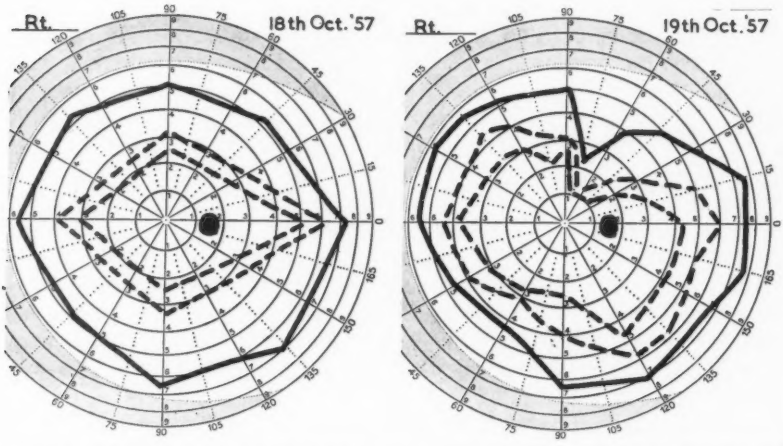


FIG. 9.—Visual fields in the right eye of Cushing's patient, as charted on October 18, 1910, and re-charted the following day at the instigation of Adolf Meyer. (From *Brain* (1921), **44**, 343.)

of the latter's patients with "uncinate" epilepsy secondary to a gunshot wound of the left eye and orbit. The missile had lodged in the petrous portion of the left temporal bone after having traversed the lower part of the temporal lobe. The field of vision of the right eye, as originally charted, showed no abnormality, but at Adolf Meyer's suggestion was

XUM

retested at 15 degree intervals instead of at the customary 30 degree intervals. Re-examination the next day then showed a narrow sector-shaped defect in the upper contralateral homonymous quadrant, just outside the vertical meridian, which is very reminiscent of the defect which we have found in our minimal hemianopias (fig. 9). It is presumably due to a lesion affecting the most anterior and ventral part of the optic radiation as it sweeps around the temporal horn.

Cushing (1921) used this particular case to introduce his classical paper on the visual field defects produced by temporal lobe lesions. Unfortunately because the patient had lost one eye, it was not possible to ascertain whether the defect was congruous or not. Cushing recorded the field defects in 10 further cases, but they were all tumours and the fields were all incongruous. Subsequently Traquair (1922) pointed out that Cushing's field defects were more likely to have been due to local pressure of the tumour on the optic tract rather than to a lesion of the optic radiation, and Traquair therefore was inclined to disbelieve the existence of Meyer's loop.

The variation in the extent of the field defect with operations of comparable magnitude requires consideration. Meyer (1911) argued that lesions of the temporal lobe must be deep and must be adjacent to the lateral ventricle before they can involve the optic radiation. The lesions produced by our operation of anterior temporal lobectomy fulfil these two criteria. The anterior sweep of the ventralmost fibres of the radiation forwards towards the tip of the temporal horn and then their horizontal course backwards, at first lateral to the temporal horn and later inferior to the ventricle, explains why these fibres are particularly liable to be interrupted by the operation so producing a congruous defect in the upper parts of the homonymous fields immediately adjacent to the vertical meridian. The range of severity of the field defects with excisions of any given magnitude is probably largely accounted for by the variations in the extent of the anterior sweep of the radiation from one person to another, as well as by variations in the size of the temporal lobe with reference to the rest of the brain. The fact that the pattern of the visual field defects shows no significant differences no matter whether the excision involves the anterior 4·5 to 6 cm. or between 6·5 and 7·5 cm. is probably explained by the horizontal course backwards of the radiation lateral to the temporal horn. As its fibres here run horizontally, as extension backwards of the incision into the temporal horn at these levels runs parallel with the radiation and does not cut fresh fibres. With removals of more than 8 cm. however, more and more fibres are cut as they begin to pass obliquely beneath the ventricle, and so severity of the field defects tends to increase.

Spalding (1952) in his paper on the effects of gunshot wounds of the optic radiation has substantiated Meyer's views, and given a description

XUM

of the optic radiation in greater detail. He has postulated that the anterior part of the radiation runs lateral to the temporal horn, and that in this part of its course the fibres subserving central vision lie in its lateral aspect, tending to congregate in the intermediate zone, while the fibres subserving peripheral vision lie on its medial aspect tending to congregate at its upper and lower margins. Our own observations on the pattern of the visual field changes following anterior temporal lobectomy lend support to his views, for it is particularly the lower margin of the radiation which is damaged by the operation.

Since our main series was collected, we have had an additional 20 cases of temporal lobectomy, and the visual field defects in these conform to our earlier findings.

Summary

The visual field changes following anterior temporal lobectomy have been reviewed in 50 patients suffering from intractable temporal lobe epilepsy. The extent of the operations ranged from 4·5 to 9 cm. as measured from the temporal pole along the infero-lateral border of the lobe. In all cases the tip of the temporal horn of the ventricle was opened into at operation.

Subsequently in each case there was a visual field defect, which in many instances was too slight to be detected by confrontation testing, but which could be elicited by quantitative perimetry. The visual field defect was always congruous affecting the contralateral homonymous fields. The extent of the visual field loss, however, varied considerably from patient to patient and had no hard-and-fast relationship to the extent of the temporal lobe removal as measured along the inferior border of the lobe.

In the slightest degrees of hemianopia the loss is apparent only in the upper part of the contralateral homonymous fields immediately adjacent to the vertical meridian. Then with ascending degrees of severity of hemianopia the loss spreads in a sector-shaped fashion towards the horizontal meridian. In the even more marked degrees of hemianopia the loss extends downwards below the horizontal meridian, again in sector shaped fashion towards the lower part of the vertical meridian. Macular vision tends to be spared except when the hemianopia is greater than a quadrant.

There are no significant differences in the range of extent of homonymous hemianopia following excisions of 6 cm. or less and following excisions of between 6·5 and 7·5 cm. The chances of there being an upper quadrantic hemianopia or less is in the order of 5 or 6 to 1. Such a degree of hemianopia usually does not inconvenience patients. With excisions of 8 cm. or more, however, the chances of a hemianopia greater than a quadrant increase and such a degree of hemianopia constitutes an appreciable disability.

XUM

These findings run counter to the prevailing view expressed in the literature (largely on observations made on tumour material) that lesions of the anterior temporal region produce incongruous homonymous field defects. Instead they lend support to Meyer's view that the lowermost fibres of the optic (geniculo-calcarine) radiation loop around the tip of the temporal horn and then pass backwards inferior to the ventricle to reach the calcarine cortex. They also reinforce Spalding's more detailed views on the anatomy of the optic radiations based on the effects of gunshot wounds.

We wish to thank Professor Brodie Hughes, F.R.C.S., for his helpful advice and interest. We also wish to thank Miss S. Treadgold, of the Department of Medical Illustration, Guy's Hospital, for copying the visual field charts.

REFERENCES

CAVANAGH, J. B., FALCONER, M. A., and MEYER, A. (1957). Communication to Second International Colloquium on Temporal Lobe Epilepsy, Washington, in press.

CUSHING, H. (1921) *Brain*, **44**, 341.

DUKE-ELDER, Sir W. S. (1949) "Text-book of Ophthalmology." London, Vol. IV.

FALCONER, M. A., HILL, D., MEYER, A., MITCHELL, W., and POND, D. A. (1955) *Lancet*, **1**, 827.

——, ——, ——, and WILSON, J. L. (1957) Communication to Second International Colloquium on Temporal Lobe Epilepsy, Washington, in press.

HARRINGTON, D. O. (1939) *Arch. Ophthal., N.Y.*, **21**, 453.

HUGHES, B. (1954) "The visual fields." Oxford.

KRAVITZ, D. (1931) *Amer. J. Ophthal.*, **14**, 781.

MEYER, A. (1907) *Trans. Ass. Amer. Phycns.*, **22**, 7.

—— (1911) *Trans. Amer. neurol. Ass.*, p. 201.

PENFIELD, W. (1954) *Brit. J. Surg.*, **41**, 337.

OLDBERG, S. (1937) *Acta med. scand.*, **93**, 330.

SPALDING, J. M. K. (1952) *J. Neurol. Neurosurg. Psychiat.*, **15**, 99.

TRAQUAIR, H. M. (1922) *Brit. J. Ophthal.*, **6**, 251.

—— (1938) "An introduction to clinical perimetry". 3rd Ed. London.

WALKER, C. B. (1917) *Arch. Ophthal., N.Y.*, **46**, 537.

THE ARCHITECTURE OF THE OPTIC RADIATION IN THE TEMPORAL LOBE OF MAN

BY

J. M. VAN BUREN AND M. BALDWIN

(From The Branch of Surgical Neurology, National Institute of Neurological Diseases and Blindness, National Institutes of Health, Public Health Service, U.S. Department of Health, Education, and Welfare)

INTRODUCTION

ALTHOUGH the general course of the geniculo-calcarine radiations in the temporal lobe has been known since the work of Probst (1906), Meyer (1907), and others, apparently little detailed consideration has been given since to the matter. Several factors have operated to promote a *status quo* in this respect. The early anatomical observations were well supported by both description and plates, and with regard to the temporal detour of the optic radiation, little was added by the later painstaking researches of Pfeiffer (1925) and Putnam (1926*a*, *b*). This has given a finality to the regional anatomy which has been perpetuated by repetition of appealing diagrams such as that of Cushing (1922) in the standard texts. Physiological evidence, however, derived from the examination of the field of vision in man has been found by many authors to disagree in some respects with the functional potentialities of the classical anatomical system.

As in all human studies correlating form and function, the accumulation of sufficient cases with an adequate anatomical control is a discouragingly slow process if the usual non-expanding lesions—which are Nature's closest approach to the laboratory lesion—form the sole basis for the study. Neoplastic material is therefore used and is open to many objections well recognized by the conscientious workers in the field. These objections force them to cautious deductions and engender little enthusiasm for a clash with well-established concepts. War injuries have provided a large volume of material which has been ably reviewed. Due, however, to the random nature of the injuries, the bursting effects of the missile (which gives little assurance that injury was only sustained in the tract of the projectile) and the difficulty in obtaining anatomical control, the conclusions must often be incomplete for fear of overstepping the bounds of proper evidence.

XUM

The present material seemed to afford us the privilege of studying a group of lesions in which many, at least, of the ideal laboratory conditions had been fulfilled. This opportunity has given us courage to re-examine the original evidence and to propose an anatomical hypothesis, which seems consistent with our evidence. If it should not stand the test of later findings and serve simply to stir study in a subject considered by many as closed, it will have fulfilled the desires of its proposers.

Material and Methods

The material selected for study consisted of 44 persons in whom the temporal lobe had been removed for the relief of epilepsy. The majority were young adults, although the ages ranged from 14 to 53 years.

The first 6 patients were operated on by Dr. Wilder Penfield and the remainder by Dr. Maitland Baldwin, The technique of temporal lobectomy in both series was essentially the same. A majority of the procedures were carried out under local anæsthesia and the removal was made by suction dissection and not by electrocoagulation methods. The degree of removal, although always progressing from anterior to posterior in the temporal lobe, varied from case to case depending upon the findings during the procedure. Thus the retention of tissue of abnormal appearance or electrical activity would prompt further resection where this were surgically feasible. In general, however, an attempt was made to limit the opening made into the temporal horn, since retention of the integrity of the ventricular system appeared to reduce the post-operative incidence of aseptic meningitis. In doing this, the ependyma and a thin layer of overlying white substance were often left intact. There was, however, no strict adherence to this technique, and when there was evidence of continued epileptic activity from deeper structures, the temporal horn was often widely opened during the subsequent removal.

Although in all cases careful surface mapping was carried out on standard brain charts, no satisfactory method was found for precisely mapping the degree of removal of intracerebral structure, due to the irregularities of the exposed surfaces and the lack of discrete landmarks. The most useful notation was usually whether or not the temporal horn had been entered. In 11 instances note was not made on this point, but in the remainder a definite statement was available.

No instance was included in which there was evidence of either hæmorrhage or tumour at the time of surgery or in the subsequent microscopic study of the excised tissue. In the case of the patient Yar the tissue was lost, but it had appeared grossly normal.

The pre-operative perimetric and tangent screen examinations were carried out by J. M. V. B. in 20 patients and perimetry only in 3 additional patients. Of the remainder, the authors wish to express their gratitude to Dr. William Feindel for perimetric and tangent screen examination of

XUM

patient, Sc, to Dr. Leonard Berg for perimetric examination of patient Cw, to Dr. Edward Laskowski for tangent screen examination of patient Mag, to Dr. William Headley for perimetry of Hag, Jo, Ni and Wa, and to Dr. Bruce Ralston for perimetry of Cl, Dr, Go, Han, Ja, Ji Ki, Mc, Ot, Ph, Se. In all instances the visual fields were found to be normal.

Two patients, Man and Mi had been operated upon by M. B. at another hospital and the pre-operative records were not available. No record of pre-operative visual testing was found in the chart of patient Hu at the time of this review, other than the bedside notation that the patient had no visual complaints and the fields were full by confrontation.

No pre-operative visual acuity was recorded in 8 cases, though fortunately for the consideration of visual acuity in this study, 7 patients had a post-operative visual acuity of 20/30 or better O.U. uncorrected. The eighth patient (Man) had severe hyperopia which could be corrected with glasses to V.O.S. 20/30, V.O.D. 20/20. Of the remaining 36 cases in which the visual acuity was charted pre-operatively, all patients had a visual acuity (with correction if needed) of 20/40 or better.

All post-operative visual fields and visual acuities were recorded by the same examiner (J. M. V. B.) with this study in view. Only patients who were fully co-operative and had an adequate attention span were considered. The earliest time selected for re-testing of the visual fields following temporal lobectomy was that point in the patient's course when he could co-operate for the entire testing period, which averaged 45 minutes. If fatigue became evident (attention variations, spiral isopters, lack of reproducibility of the isopters) the testing was terminated, the results discarded and testing undertaken at a later time when more reliable results could be obtained. An attempt was made to examine patients as late in their hospital stay as possible and at subsequent clinic visits. Table I indicates the days elapsing between operation and examination.

TABLE I.—THE PERIOD FROM TEMPORAL LOBECTOMY TO VISUAL FIELD EXAMINATIONS

	NIH series	*MNI series*	*Totals*
1–9 days	1	—	1
10–19 days	17	5	22
20–29 days	9	—	9
30–39 days	1	—	1
127–829 days	18*	1	8
Total	35	6	41

*11 of the 18 cases had been initially examined at an earlier hospital admission.

Although the majority were examined less than 30 days following surgery, it was possible to examine 18 individuals following a post-operative period of four to thirteen months. Both initial and subsequent (four to nine months later) examinations were obtained in 11 of these patients.

XUM

The first 6 cases were examined at the Montreal Neurological Institute. The visual acuity at 20 feet was determined both with and without visual correction if used. The patient was then seated in a chair with an occipital headrest at a 2 metre distance from the tangent screen and the visual field for the central 25 degrees of vision obtained, including the blind spot which was outlined with a 3/2,000 white object. The screen was brightly lit by flood lamps. In retrospect, it probably was considerably brighter than necessary as the incident light varied from 200 to 350 foot candles. At the start the subject's eyes were carefully observed by an assistant to assure constant fixation. It became apparent, however, that movements of even 5° were difficult to detect with certainty, and since the reproducibility of the isopters[1] was the final proof in any case, this method was abandoned. When a defect was found not only were the individual isopters rechecked, but by the use of at least 4 and often 6 test objects with extensively sloping defects, the final charting was thought to be consistent within the limit of error of the method. This error, as judged by comparison of the results of charting of the same individual at different times, could amount to as much as 5° for a given isopter though it was usually less. Reference to Table II indicates that with a totally dense defect with sharp margins, such as the blind spot, patient co-operation was sufficient to show a maximum variation at two separate examinations of only 4 cm. at 1,000 mm. distance or to represent 2° 18′ of arc. The reproducibility of a defect with sloping borders would be expected to be more difficult for the patient and thus result in a greater variability. Following the tangent screen examination, the patient was seated at a 330 mm. perimeter and the peripheral fields defined usually using 1 and 3 mm. white objects.

The last 35 patients were examined at the National Institute of Neurological Diseases and Blindness and a similar technique followed with the exception that tangent screen examinations were carried out at a 1 metre distance and the incident screen illumination was rather more even and varied from 25–29 foot candles. The blind spots were charted with a 3/1,000 white object. Throughout the study it became increasingly apparent that the tangent screen offered the most useful information so that proportionately greater time was spent with this method, and in the

[1]As an object of proper and specific size and luminosity is brought out of the blind periphery toward the centre of gaze, or from any area of reduced vision in the visual field, it becomes visible at a point which may be indicated on the visual field chart. An "isopter" is defined here as the line formed by joining these points of liminal visibility. When a number of isopters for objects of differing size and/or luminosity are charted, they may be compared to contour lines upon the map of a mountain. Concentric contour lines and isopters when closely grouped indicate a steep grade; or, as used here "slope" while in those areas where the same isopters (or contour lines) are wider separated a gentler and less distinct slope is indicated. Viz Traquaire (1949) Chap. I.

XUM

last 15 cases only one isopter was charted with the 330 mm. perimeter. In instances where the temporal horn had been opened but no visual field defect was apparent on initial examination, the room illumination was further lowered. In one instance, this resulted in the discovery of a minimal defect (Case Ot).

Of the 44 cases initially thought suitable for this study, 43 were consecutive cases selected only in that they fulfilled the criteria mentioned above. 3 cases were eliminated on final consideration as doubts had been noted upon the visual field chart as to the degree of the patient's cooperation, and it seemed well to eliminate questionable records. The last case was included after the series was terminated, since it was a

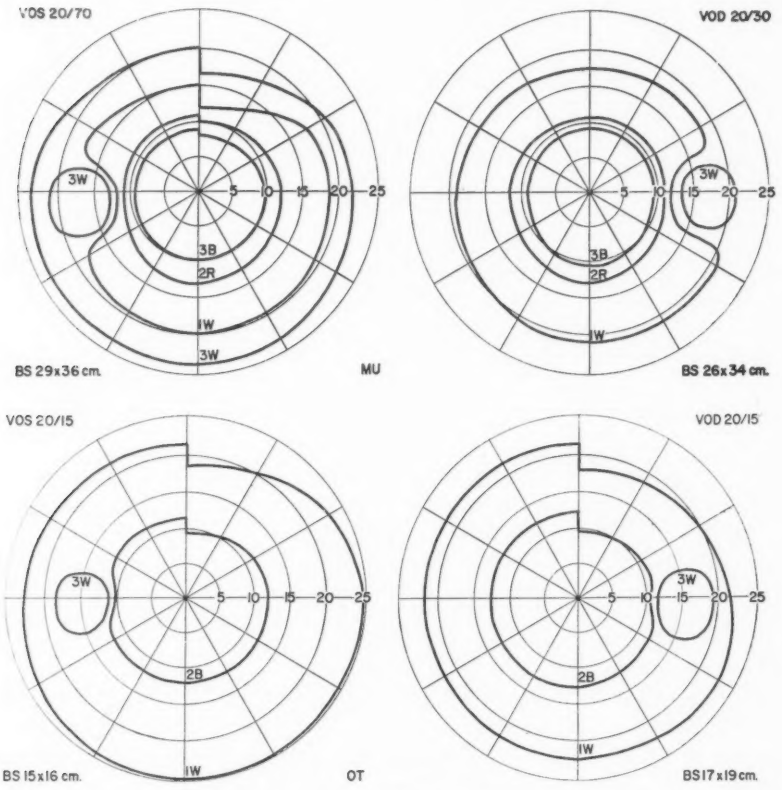
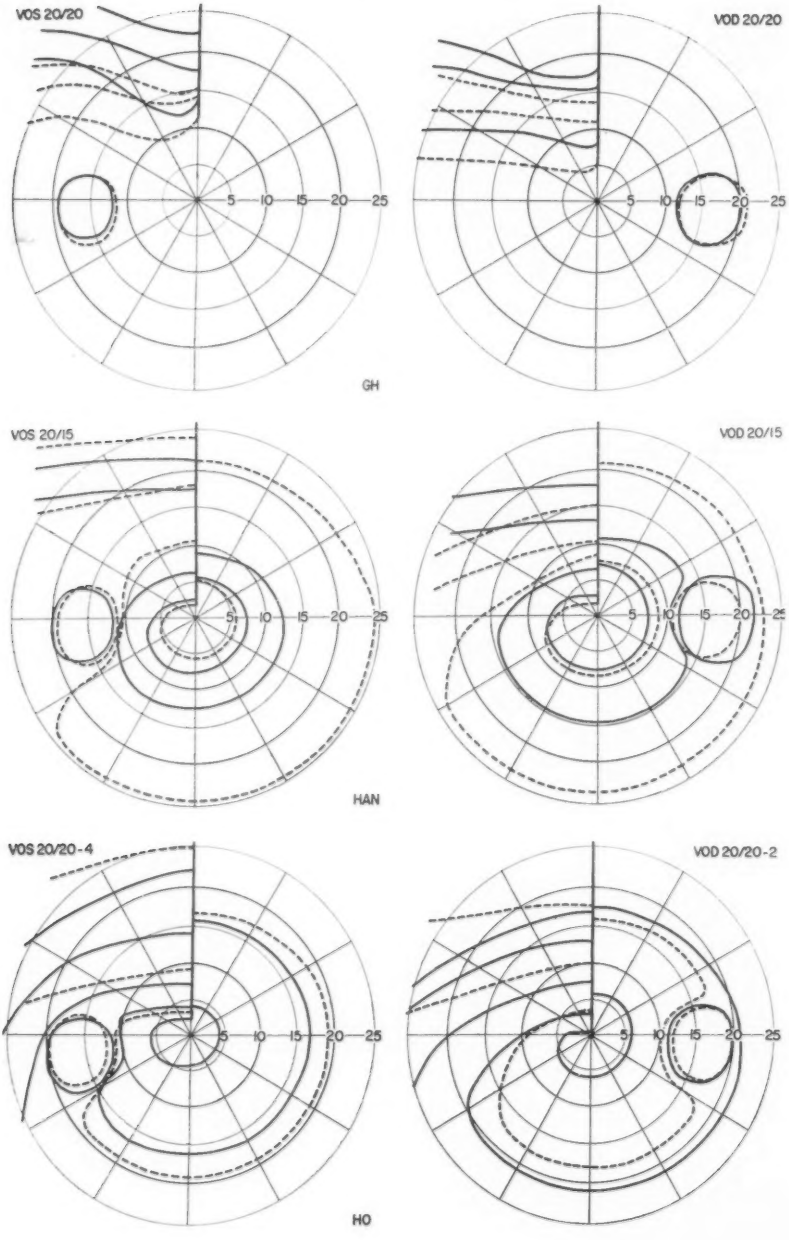


FIG. 1.—Two minimal visual field defects following left temporal lobectomy. Mu was charted at 2,000 mm., twelve days after operation; Ot was charted at 1,000 mm. nine days after operation. Both defects proved to be transient. Mu was the only case showing a visual defect in only one eye following temporal lobectomy.

XUM


VOS 20/20
5
10
15
20
25
VOD 20/20
5
10
15
20
25
GH
VOS 20/15
5
10
15
20
25
VOD 20/15
5
10
15
20
HAN
VOS 20/20-4
5
10
15
20
25
VOD 20/20-2
5
10
15
20
25
HO

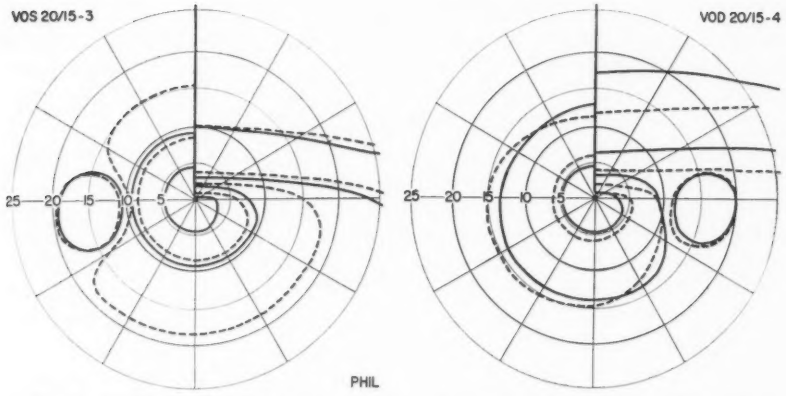


FIG. 2.—Four examples to illustrate the relative stability of visual field defects following temporal lobectomy. Gh 1 mm. white, 5 mm. blue, and 3 mm. white objects at 1,000 mm. (Gunkel self-recording tangent screen) 33 days and 67 days after operation; Han 2B, 1W, 3W, 18W at 1,000 mm.; 23 and 179 days after operation; Ho 2B, 1W, 3W, 6W, 18W at 1,000 mm.; 14 and 173 days after operation; Phil 2B, 1W, 3W, 18W at 1,000 mm.; 24 and 186 days after operation. The isopters charted on the earlier examination are indicated by dashed lines.

further example of amputation of the white substance covering the tip of the temporal horn with free opening into the ventricle without visual field defect, and hence, was of considerable theoretical interest. Thus the number of cases of visual field examination following temporal lobectomy properly included in this study number 41.

RESULTS

The Stability of Visual Field Defects Following Temporal Lobectomy

Since during temporal lobectomy by this technique operative injury to the optic pathway could directly approach only from the anterior and/or lateral aspects of the temporal loop, it seemed important to attempt, at least, to determine how much extraneous processes, such as œdema or inflammatory reaction might modify the observed changes in the visual field. A direct answer to this problem, was, of course, not available but a clinical meningitis[1] was observed but once and œdema is presumably a reversible process. In 11 patients examination both in the immediate post-operative period and four to nine months following surgery was possible. Patients Mu and Ot demonstrated transient defects, that of the former, disappearing five weeks following surgery and that of the latter

[1]Patient Wil twelve days following surgery developed fever and nuchal rigidity. This proved to be an aseptic process associated with gross xanthochromia of the spinal fluid and he recovered promptly.

XUM

was not detectable on a clinic visit four and a half months after temporal lobectomy. The visual fields of these patients are given in fig. 1 and the lack in each of a dense field defect is apparent. The 10 remaining patients in whom examination had been repeated four to nine months after surgery showed dense defects and the examples shown in fig. 2 were quite typical of the group. In these cases there was a slight tendency for peripheral recession of the isopters, but this in no case averaged over 5°. This, however, was not invariable as some showed a constriction of the isopters at the later examination of nearly a similar degree. The relative stability of the major visual field defects has encouraged us to believe that we are witnessing the effects of surgical ablation and not œdema of the temporal portion of the visual radiation. This assumption and the fact that the temporal portion of the visual pathway can only be reached surgically from its anterior and/or lateral aspect (i.e. not from the medial aspect) are two important points for consideration in formulating the anatomical hypothesis to be discussed below.

Negative Findings

(1) Visual acuity: The visual acuity was found to be essentially unchanged by temporal lobectomy. As mentioned above, 7 of the 8 instances in which the visual acuity had not been recorded pre-operatively, had a post-operative uncorrected visual acuity of 20/30 or better and in the last instance, near normal vision could be achieved by proper glasses. In all but one of the remaining 33 cases the variation between the pre-operative and post-operative testing amounted to less than a line on the standard 20 foot testing chart, and the variations fell equally in a positive or negative direction. In Case Co, the vision of the left eye fell from 20/30–2 to 20/50, although the vision of the right eye remained constant at 20/30 both before and after operation.

In 2 cases, not included in this series, a macula-splitting homonymous hemianopia with complete visual loss up to 0–2 degrees of the fixation point on various testings was found after a radical temporal removal. Case Un (fig. 3) is an example of one of these, and since the head was allowed free during this examination, the compensatory head tilt is shown as well. In both cases despite the macula-splitting nature of the hemianopia, the visual acuity had remained completely unchanged from the pre-operative record.

(2) Blind spot: Pre-and post-operative records of the measurements of the blind spots were available for 11 patients (Table II). It will be noted that as many measurements were increased as were diminished following operation. The maximum variation of the blind spots as tested at 2,000 mm. was 7 cm. (2° 1′) and 4 cm. at 1,000 mm. (2° 18′). These figures, although affording only negative evidence regarding the blind spot, were

XUM

considered important in assessing the overall co-operation and reliability of the patients in this group, and they are believed to be representative of the entire series.

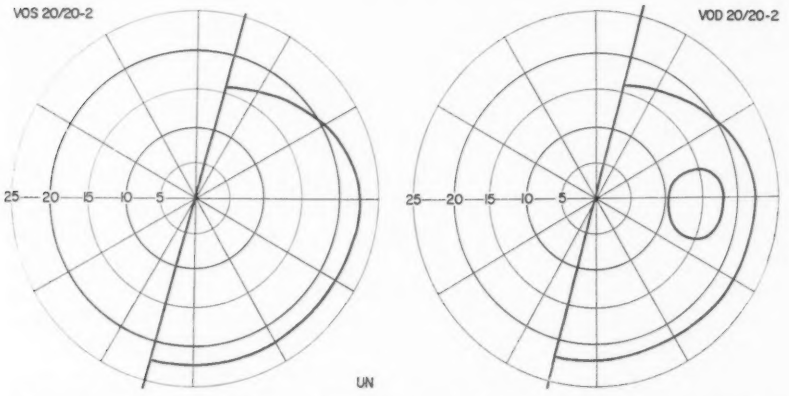


FIG. 3.—The macula splitting defect and head tilt resulting from a far posterior temporal lobectomy. Note visual acuity was unchanged. 1W and 3W (for blind spot) at 1,000 mm. Hemianopia absolute for objects up to 200 mm.

TABLE II.—THE MEASUREMENTS OF THE BLIND SPOTS IN 11 CASES BEFORE AND AFTER TEMPORAL LOBECTOMY

	Pre-operative				*Post-operative*			
	O.S.		*O.D.*		*O.S.*		*O.D.*	
Patient	*Trans-verse*	*Vertical*	*Trans-verse*	*Vertical*	*Trans-verse*	*Vertical*	*Trans-verse*	*Vertical*
Ad	14	17	14	17	16	18	17	19
Co	16	18	17	19	16	17	15	17
Ga	17	18	16	18	18	20	17	19
Ka	14	18	13	16	12	14	12	14
Me	16	18	16	18	16	19	17	22
Sm	12	16	14	17	16	18	16	20
Ta	19	19	18	20	16	17	16	17
Va	13	14	11	14	12	16	14	16
Wil	15	20	14	19	15	17	15	17
Wim	14	18	16	18	15	18	15	17
Ya	14	18	15	18	15	18	16	21

Measurements are given in centimetres as charted with a 3 mm. white object at 1,000 m. In addition to the fact that the measurements of the blind spots were not consistently changed by interference with the optic radiation, it may be noted that the reproducibility of a visual field defect with these patients showed a maximum variation of 2° 18′ (4 cm.).

XUM

(3) Monocular Crescent: Examination of the far periphery of the visual field with the 330 mm. perimeter failed to give any evidence of selective sparing of the monocular crescent when defects of the visual field were encountered nearer the fixation point along the same testing radius. It may be noted, however, that in general the largest test object used at this distance was a white 3 mm. target (0° 30′) so the evidence may not be adequate, although to prove density in the central 25° field often a white 200 mm. target at 1,000 mm. (11° 30′) was used without peripheral sparing being reported by any patient.

Positive Findings

(1) The relationship between the intactness of the tip of the temporal horn and the visual field defect: In 33 patients a statement was available in the operative record as to whether or not the tip of the temporal horn had been opened. 6 cases (Ad, Dr, Ka, Jo, Se Wa) lacked a demonstrable defect of the visual field post-operatively. The temporal horn was not opened in patients Ad and Wa. In the instance of patient Dr, question was raised as to the possibility that the temporal tip might have been opened, since at one point in the procedure a gush of clear fluid suddenly appeared at the deepest point of the excision. The horn was definitely opened in patients Jo, Ka and Se and in Jo the anterior half of the pes hippocampus was removed with consequent excision of the ventricular wall back to level of the transverse plane defined by this removal in the pes. These last 3 patients were a most interesting group and were examined under diminished illumination with more than the usual care without the discovery of any visual deficit. All 3 were examined between 16 and 21 days following surgery. Both of the transient minimal defects (Mu, Ot, fig. 1) had had the temporal horn opened, and in the former the tip had been widely excised. In the case of Ot, the original defect was only detected by tangent screen examination with reduced illumination. It thus appeared that in 5 cases, at least, the tip of the temporal horn, and its surrounding white substance, could be removed without a permanent detectable change in the visual field.

Conflicting evidence (i.e. the post-operative presence of visual field defects in patients whose temporal horns remained unopened) was present in 6 cases (Ba, Go, Me, Ta, Van, Wim). Because opening of the ventricle was avoided when possible by carefully sucking off the cerebral substance from the ventricular lining, the validity of this evidence for anatomical considerations was considered of little moment. It seemed not unreasonable to believe that damage to the geniculo-calcarine pathway, which lies in the white substance a few millimetres outside the ventricle, might well occur when the ventricular lining itself had not been perforated.

(2) The results of further excision following an earlier lobectomy: 3 patients (Phil, Kin, Hu) were examined both before and following

XUM

additional resection of the temporal lobe because of continuing epileptic activity in this region. Fig. 4 shows a result of this further procedure and

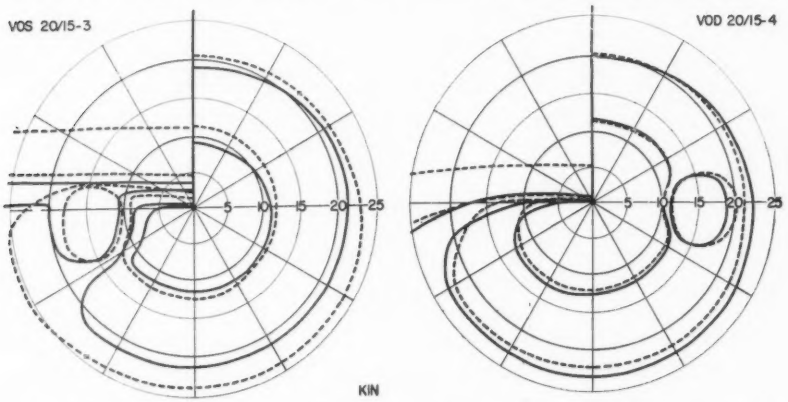


FIG. 4.—Dashed lines indicate isopters 656 days after temporal lobectomy; solid lines indicate isopters 13 days after a further removal. Note that after revision the isopters crowded closer to and tend to overstep the horizontal meridian. 2B, 1W, 3W, 18W, at 1,000 mm.

is quite typical of the others. The visual acuity was unaffected and it will be noted that the form of the visual field defect was not charged by further excision other than having the slope of the inferior margin increased a bit and this margin slightly displaced downward. None of the cases with a slanting inferior margin (*see below*, section 5 and fig. 9) were subjected to a further temporal removal.

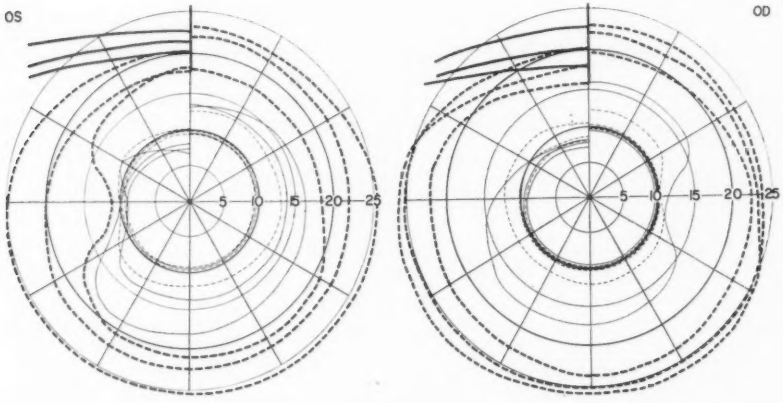


FIG. 5A.

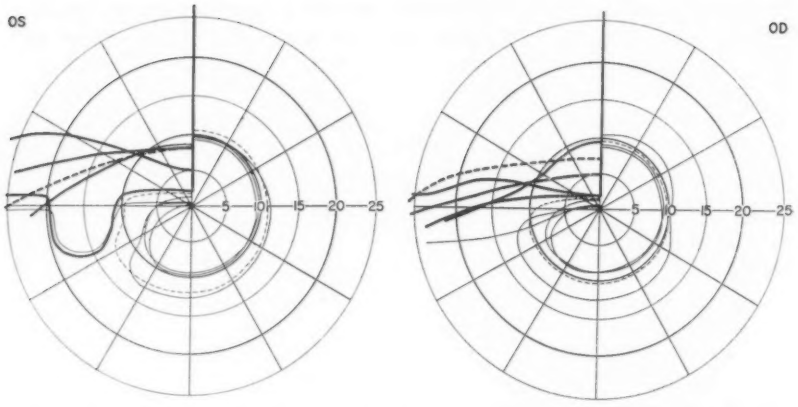


FIG. 5.—A, Simultaneous charting of the isopters with the largest (3W) and smallest test objects employed in the 6 minimal defects; B, Simultaneous chartings of the isopters with the largest and smallest test objects in the 5 maximal quadrantic defects following temporal lobectomy. The dashed isopters had been observed following left temporal lobectomy and are here transposed to facilitate comparison.

(3) The relationship of the visual field defects to the fixation point: In all cases, the visual field defect closest approximated the fixation point along the superior vertical meridian. As illustrated in fig. 4 (Kin), this approximation of the defect to the fixation point might be very close indeed. This relationship to the fixation point may be seen in fig. 5, in

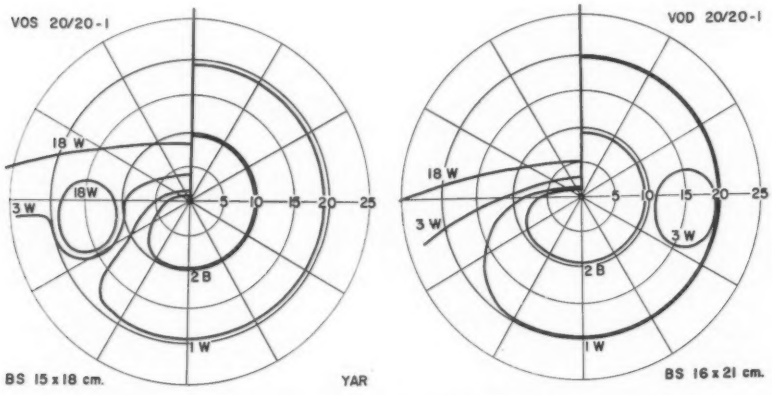


FIG. 6.—A rather typical example of the defect following right temporal lobectomy as charted at 1,000 mm. Note the normal visual acuity, the sloping margins of the defect which extend over the horizontal meridian and the finding of a larger defect in the visual field of the right eye.

which the least and largest isopters in cases showing minimal and maximal defects are simultaneously charted.

(4) The margins of the visual field defects: fig. 6 (Case Yar) is a typical example of the sloping nature of the inferior margin of quadrantic defects following temporal lobe excision. The depression of visual acuity in the peripheral field on the side of the quadrantic defect appeared to be a general one for test objects of all sizes and colours, i.e. all isopters would be displaced toward the fixation point and the horizontal meridian.[1]

In the more severe defects, such as Case Kin (fig. 4), it will be seen that the slope of the inferior margin of the defect was increased and the isopters tended to group themselves closer to the horizontal meridian. The horizontal meridian was not, however, inviolable and could readily be overstepped inferiorly by the smaller isopters. The varying slope of the inferior margin, with defects of differing extent, may be seen by comparison of examples in fig. 5, in which the cases showing minimal and maximal defects are superimposed.

In all cases, the medial margin of the defect along the superior vertical meridian was sharp to all test objects, i.e. the variation of the various isopters was found to be at a maximum 3° and was usually less. Occasionally the medial aspect of the quadrantic defect did not precisely correspond with the vertical meridian—a variation which did not seem secondary to head tilt and proved reproducible in testing. Since there are so few straight lines in Nature, it is perhaps more remarkable how, in most cases, the medial margin of a post-chiasmal visual field defect will so nearly approach a truly straight line that parallels the vertical axis of the head.

(5) The forms of visual field defect following temporal lobectomy: The 33 patients who showed persistent major defects of the visual field following temporal lobectomy could be divided into two groups. 10 (fig. 7) demonstrated homonymous *congruous* quadrantic defects. 23 (fig. 8) were found to have homonymous *incongruous* quadrantic defects *with the defect closer approaching the fixation point in the eye on the side of the temporal lobectomy*. No instance was observed in which an incongruous defect approached the fixation point closer in the eye contralateral to the temporal lobectomy.

Although the majority of the 33 patients with visual defects showed a striking tendency for the inferior margin of the defect to parallel the horizontal meridian, a significant number (Ba, Gh, Ni, Ow, Ji, Van) exhibited a slanting inferior margin, which closest approached the

[1]At times with the same coloured object the isopter for form recognition and that for colour recognition were separately charted. Although the two isopters obviously didn't coincide, if a defect was present, it was found to be present in both.

XUM

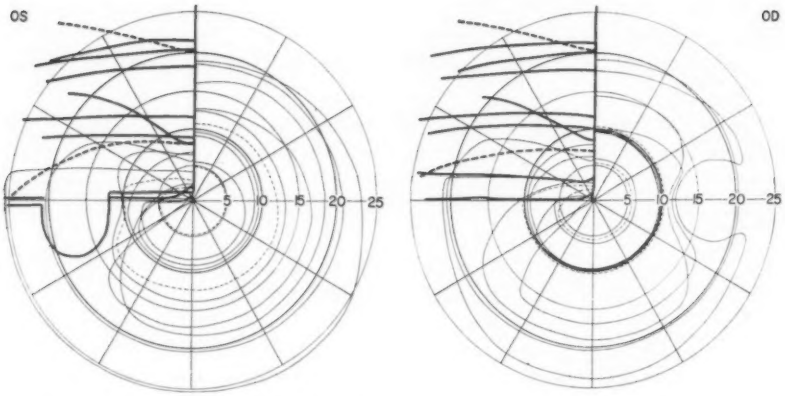


FIG. 7.—Simultaneous charting of the isopters with the largest and smallest test objects employed in 10 cases exhibiting congruous defects of the visual field following temporal lobectomy. The dashed isopters had been observed following left temporal lobectomy and are here transposed to facilitate comparison.

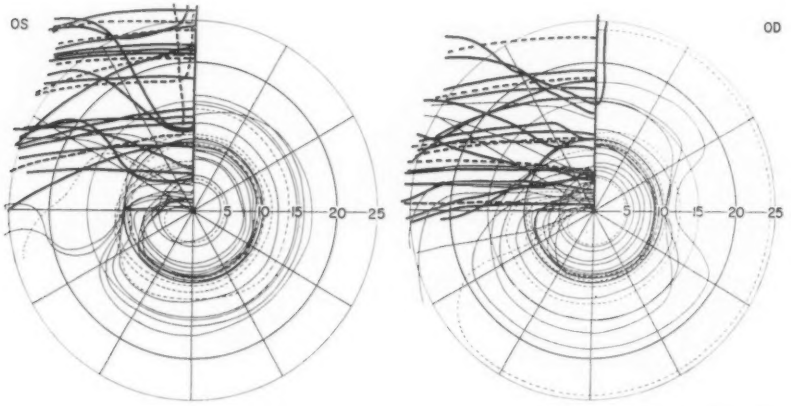


FIG. 8.—Simultaneous charting of the isopters with the largest and smallest test objects employed in 23 cases exhibiting incongruous defects of the visual field following temporal lobectomy. The dashed isopters had been observed following left temporal lobectomy and are here transposed to facilitate comparison.

horizontal meridian directly above the fixation point (fig. 9). The defects might be either congruous or incongruous and the inferior, or rather inferior lateral margins of the defect sloped in the same fashion as the defects, which had a roughly horizontal inferior margin.

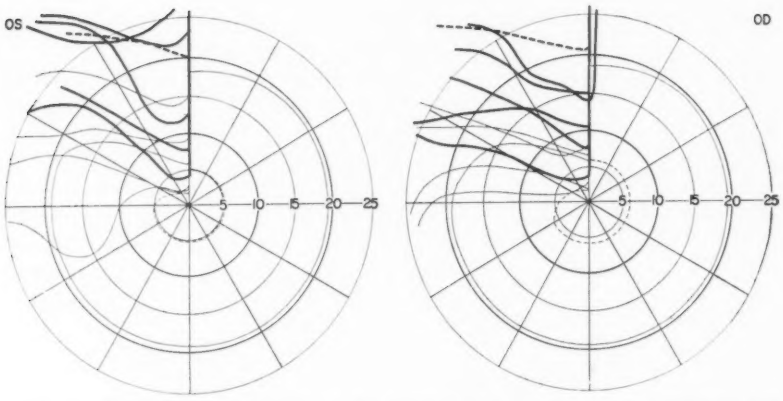


FIG. 9.—Simultaneous charting of the isopters with the largest and smallest test objects employed in 6 cases in which the isopters closest approached the horizontal meridian in the region of the vertical meridian. Both cases with congruous and incongruous visual field defects are included. The dashed isopters had been observed following left temporal lobectomy and are here transposed to facilitate comparison.

DISCUSSION

A. *Physiology of the Human Optic Radiation in the Temporal Lobe*

(1) The relationship of homonymous upper quadrantanopias to the fixation point, and the nature of their margins with regard to both location and density.

There seems no substantial evidence to indicate that loss of one half of this visual system will decrease the acuity of the adjacent intact portions of the system or affect the recorded visual acuity. Our 2 cases of complete macula-splitting hemianopias and unchanged visual acuities following a radical temporal removal substantiate this. Although Lillie (1925) found some visual impairment in 19 of 32 patients with temporal lobe tumour the majority were ascribed to obvious optic atrophy. This retention of visual acuity provided one half at least, of the visual system is intact, although a commonplace with lesions of the suprageniculate optic system may be seen with lesions placed farther forward. Rönne (1927) even reports that occlusion of a peripheral branch of a retinal artery may truly destroy a half of the macula and yet the patient retain fully normal visual acuity in the functioning macular half.

In view of the retention of normal visual acuity with massive lesions of the visual system, it would seem unlikely that the visual acuity would change after a lesion of the optic radiation in which only a quadrant or less of the visual field had been rendered functionless. This has been the case in the present series, and, curiously enough, the loss of the homonymous upper

quadrant of gaze was unknown to the majority of patients at the time of testing. We have yet to hear a patient complain of this loss or even spontaneously to mention it. Holmes (1918) reported a similar lack of a subjective scotoma in a man (Case 15) in whom a war wound produced a homonymous upper quadrantanopia found by scotometer to extend to the fixation point. Although this may presumably be related to the small use we make of the upper half of the field of vision, it remains an interesting point which has attracted very little attention.

Much time has been spent discussing the relationship of hemianopic visual field defects to the macula and whether or not the fixation point may truly be bisected or "split" by a lesion of the suprageniculate visual pathway. The evidence has been confused by varying and all too often inadequate testing techniques and by a failure to define what is meant by a "split" fixation point with the method of testing employed by the particular examiner. Halstead *et al.* (1940) using a most elaborate method to insure adequate ocular fixation during tangent screen examination found that both macula-splitting and macula-sparing hemianopias could result following occipital lobectomy for tumour so the matter seems far from settled.

Regarding lesions of the temporal lobe, both Traquair (1922) and Cushing (1922) found that half of their temporal tumours producing hemianopic defects showed bisection of the fixation point by the blind field. Horrax and Putnam (1932) found that visual field defects extending to the fixation point were more frequent in temporal (i.e. anterior) as opposed to occipital lesions of the optic pathway and Penfield (1940) supports this observation. Quadrantic defects from temporal lobe lesions have similarly been found to vary. Holmes (1918) found that quadrant defects might or might not extend to the fixation point and the quadrantanopia following temporal lobectomy for tumour cited by Fox and German (1935) came no closer that 4° from the fixation point. In our material, the visual defect closest approached the fixation point along the vertical meridian, a phenomenon to which no exception was seen. The defect, however, might lie at nearly any distance from the fixation point from very nearly touching it (fig. 4, Kin) to a bare indication that a defect was apparent (fig. 1, Mu, Ot). This relationship of the defect to the fixation point seemed so constant (i.e. always coming closest near the vertical meridian) that it cannot be disregarded in any anatomical arrangement under consideration.

The monocular crescent corresponding with the extreme periphery of the temporal field has received relatively recent consideration by Ask-Upmark (1932) and Bender and Strauss (1937). Earlier references in which the visual field defect was found to have maximal size and density in the homonymous upper quadrants, and peripheral but not central sparing of the lower quadrant, were recorded by both Harris (1897), who

provides even earlier references and Rönne (1915). Unfortunately, little consideration in many references has been given the location of the causative lesion. Local cortical lesions of the occipital pole as Holmes (1918) with subsequent investigators has shown, can produce central loss of vision with sparing of the periphery. So far as the authors are aware, this has not been reported with a verified lesion of the anterior part of the visual radiation, and it has not appeared in our experience to date. The explanation of this may logically lie in the compactness of the radiation anteriorly, giving less opportunity for lesions to injure discretely a small enough fragment to produce a result of this kind.

Investigation of the nature of the margins of a visual field defect has largely followed the careful techniques of quantitative perimetry advocated by Cushing and Walker (1915) and by Traquair. In the latter's study of the quadrantic defects of the visual field resulting from tumours of the temporal lobe, he commented upon the fact that at the lower margins of the defect the isopters tended to separate, i.e. the margin was found to "slope" rather than to stand as a blind area with identical margins to test objects of all sizes. Basing his conclusion on his own material, Traquair (1922) was of the opinion that this sloping edge was the result of relative ischæmia caused by compression of the visual pathways at the margin of the tumour. Cushing and Walker (1915) had previously suggested that relative ischæmia might be responsible for the sloping margins of visual defects further anteriorly in the visual system. As far as is known, the reason for the sloping nature of the margin of the defect has not been discussed by other authors. Since, in our cases, there was no question of pressure and the sloping nature of the field defect remained over the months, Traquair's explanation would seem to be inadmissible.

Since a neuronal pathway must either transmit fully or not at all, partial vision must be explained on the basis of fewer units than normal participating in the act. Therefore, the partial inactivation of a neural pathway by a surgical lesion implies that all the units were not destroyed and the conclusion seems inescapable, that those which remained were *spatially* separated from those which were destroyed. In short, this indicates that *all fibres derived from a given retinal point do not lie close together in the optic radiation.* Were this dispersion of conducting fibres not present in the optic radiation the defects resulting from their destruction would be as sharp-edged and dense as the blind spot or a complete destructive lesion of the retina itself.

The common tendency for the *dense* or completely blind portions of quadrantic field defects not to overstep the horizontal meridian is a finding early pointed out by Holmes (1918) and later confirmed by Rönne (1927) among others. This, not unreasonably, caused them to suspect that anatomical separation of the quadrantic representations occurred in the

XUM

optic radiation and to postulate that the macula representation lay between the fibre bundles from the upper and lower quadrants. Defects involving or centred upon the horizontal meridian have been, however, reported by McConnell (1933) and by Spalding (1952) following war injuries. A similar defect was reviewed by the present author (Case O'Br) in which a resection by W. P. was carried out for epilepsy. In McConnell's and the author's case the defect did not approach closer than 10 degrees to the fixation point, while in one of Spalding's cases it came to the centre of gaze. The margins (in these cases both upper and lower) were found to slope in a fashion similar to the commoner quadrantic defects. This demonstration of the possibility of visual defects of the horizontal meridian plus the variability of their approach to the macula supports Spalding's contention that in the central portion of the optic radiation (i.e. a point half-way between the superior and inferior margins of the radiation), there is representation of the peripheral horizontal meridian with the horizontal portion of the macula representation lying immediately medial to this. The fact that the sloping inferior border of a quadrantic defect more frequently than not oversteps the horizontal meridian for smaller isopters (e.g. fig. 10 from Cushing, 1922) likewise suggests a contiguity of the adjacent radial sectors of the peripheral field, and is against an anatomical separation of the representation of the upper and lower quadrants of the visual fields in the optic radiation by the macular fibres.

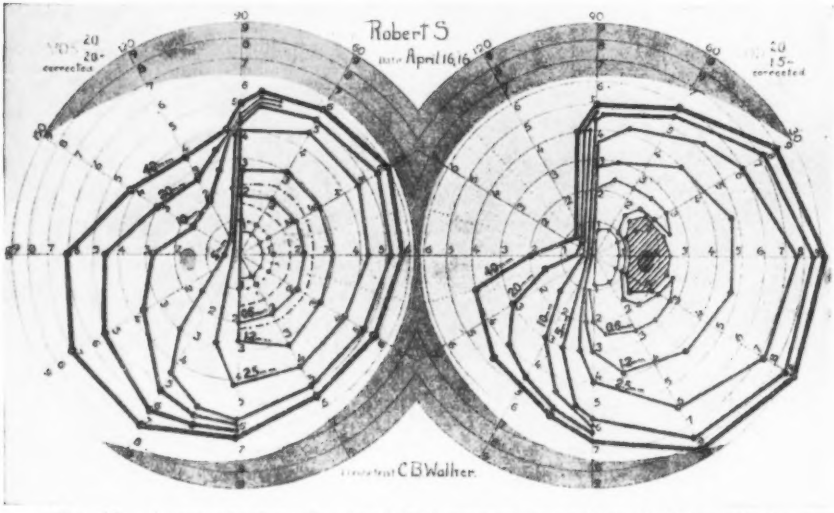


FIG. 10.—A reproduction of a visual field reported by Cushing (1922) which shows the typical features of destruction of the temporal portion of the optic radiation and may be compared with fig. 6.

(2) The symmetry of quadrantic defects of the visual field associated with temporal lesions and its significance.

The question of congruity in visual field defects is obviously of great importance from the point of view of the anatomical distribution of fibres in the visual pathways. There seems little doubt that lesions affecting the occipital portions of the visual system produce entirely similar defects of the visual fields on examination of both eyes when the patient is co-operative. This is substantiated by the pioneer work of Holmes and Lister (1916), Holmes (1918), Riddoch (1917), to name but some of the important work done with non-neoplastic material. The anatomical corollary of these observations must be that in the posterior portions of the optic system, fibres from homologous areas of two retinæ must lie side by side. By degeneration studies it is well established that separate cell layers in the lateral geniculate body receive fibres from the two separate retinæ. However, as far as it is known to the present authors the point in the optic radiation of juxtaposition of fibres from homologous points remains obscure (cf. Traquair, 1922; Rönne, 1927). Apparently thinking on the subject has been profoundly influenced by the evidence secured from occipital lesions of the visual pathway and the assumption that juxtaposition of homologous retinal fibres must occur at the lateral geniculate body or even the optic tract has followed but is apparently without either physiological or anatomical evidence as a basis. Despite this lack of direct evidence, as late as 1933 Traquair declared, "All hemianopias due to a suprageniculate lesion must be congruous."

The fact that homonymous upper quadrantic defects of the visual fields may be incongruous has been frequently observed (fig. 10) with lesions of the temporal lobe and in the majority the visual field defect is larger in the eye on the same side as the lesion (Schirmer, 1912; Rönne, 1919; Cushing, 1922; Traquair, 1922; Horrax and Putnam, 1932; Mackenzie *et al.*, 1933; Globus and Silverstone, 1935; Oldberg, 1937; Harrington, 1939). However, it has been found (Cushing, 1922; Bender and Strauss, 1937; Sanford and Bair, 1939; Harrington, 1939) that incongruous defects of the visual fields may also appear larger on the side contralateral to the cerebral lesion. Much of this work is open to criticism in that the visual fields were usually examined only by a perimeter in very ill patients. Harrington (1939), however, had apparently done multi-isopter tangent screen examination of his cases and although the cases were not directly referred to in his report, he mentioned that he had observed a homonymous upper quadrantic defect larger in the eye contralateral to the lesion. Holmes (1952, p. 117) more recently has written with regard to the visual field deficit that ". . . when the radiations are involved it is occasionally incongruous and is then usually greater in the opposite eye in which the temporal field is lost." Our failure to observe a single case of a larger quadrantanopia in the eye contralateral to temporal lobectomy has made us

XUM

somewhat doubtful of how much weight this evidence, based upon neoplastic material, can be given.

Explanations of the origin of incongruity of the homonymous quadrantanopias associated with lesions of the temporal lobe may be roughly divided into groups according to the level thought to be damaged in the visual system. Basing his reasoning upon an analogy with incongruent defects found to result from lesions in the vicinity of the optic chiasm. Rönne (1915, 1927), considered that incongruence from lesions of the temporal lobe was due to involvement of the optic tract though pointing out that detailed anatomical knowledge of the architecture of the optic radiations was very small. Traquair (1922, 1933), apparently accepted this explanation and concluded (1933) "Since the optic tract lies immediately beneath the temporal lobe, it seems justifiable to suppose that this is the part of the visual pathway which is affected to produce incongruous visual field defects with temporal tumours as the incongruity of the field defects would, on this assumption, offer no difficulty." Oldberg (1937) considered that incongruence of the visual field due to selective compression of portions of the optic tract to be unlikely, reasoning that pressure should be equally transmitted to all parts of the optic tract. Basing his hypothesis on the case of Abbie (1933) and Mackenzie *et al.* (1933) in which incongruous defects of the upper quadrants of the visual field were associated with degeneration in the lateral portions of the geniculate bodies, he concluded that ischæmia from pressure inactivating the lateral aspect of the geniculate body by tumour could produce a similar effect upon the fields of vision. Sanford and Bair (1939) appeared content with the assumption that tract interference was responsible for the incongruity of the quadrantanopias associated with lesions of the temporal lobe when the larger defect appeared in the eye ipsilateral to the lesion. To explain their findings of quadrantic defects larger in the contralateral eye, they postulate that the crossed optic fibres run a more anterior and lateral course in the initial portions of the optic radiation, and so are more exposed to damage from a lesion impinging upon the radiation from its lateral aspect. They cite no further evidence for the latter explanation. Although their work was based upon 211 tumours of the temporal lobe, apparently only 8 cases were examined by perimeter and tangent screen. It appears that Harrington (1939) also broke with tradition and concluded that incongruity of the visual fields could best be explained by dissociation of homologous visual fibres from the two eyes in the optic radiation. To support this, he cited (1) the frequency with which asymmetry is reported with temporal lobe lesions while symmetry of the defects is the rule with lesions of the occipital lobes; (2) asymmetry of the resulting quadrantanopia may be seen with non-expanding lesions of the temporal lobe; (3) following removal of the causative agent an asymmetric defect of the visual field may persist.

XUM

Although as mentioned above, some reservations may be found in the literature, it seems justifiable to draw the following conclusions regarding the functional nature of the visual fibres affected by lesions of the temporal lobe in man:

A. Visual acuity.

(1) Lesions causing either partial or complete hemianopias do not alter visual acuity.

B. Characteristics of the homonymous quadrantanopias

(1) The relationship of the defect to the fixation point.
   (*a*) The degree to which the defect may approach the fixation is variable.
   (*b*) The visual defect closest approaches the fixation point in the region of the vertical meridian.

(2) The outline of the margins of the defect.
   (*a*) The medial margin is usually vertical.
   (*b*) The inferior margin in all cases parallels a meridian of the upper quadrant passing through the fixation point and usually is horizontal.

(3) The density of the margins of the defect.
   (*a*) The isopters superimpose on the medial margin.
   (*b*) The isopters are separated on the inferior margin with the density of the defect changing in a direction perpendicular to a meridian through the fixation point.

(4) The congruity of the defect.
   (*a*) The defect may be congruous.
   (*b*) The defect may be incongruous, but if so, it is larger in the eye on the side of the lesion.

C. The relationship of the most anterior extremity of the temporal portion of the optic radiation and the temporal horn.

   (*a*) The tip of the temporal horn may be surgically excised without producing a detectable change in the field of vision.

Any anatomical hypothesis regarding the architecture of the temporal portion of the optic radiation must take into account these facts and, in the present material, the direction in which injury might be inflicted upon the optic radiation in the temporal lobe, (i.e. only from the anterior and lateral aspects).

(B) *Anatomy of the Human Optic Radiation in the Temporal Lobe*

The relationship between the optic radiation and the temporal horn has now been under discussion a half century. Meyer in 1907 described the anterior migration of the inferior portion of the optic radiations but did not then state precisely how far forward the radiations extended.

XUM

Archambault (1909) also noted this anterior deviation of the optic radiation and referred to his earlier writing on the subject in 1906. Cushing (1922) extended this evidence in his diagram (fig. 11) to show the optic

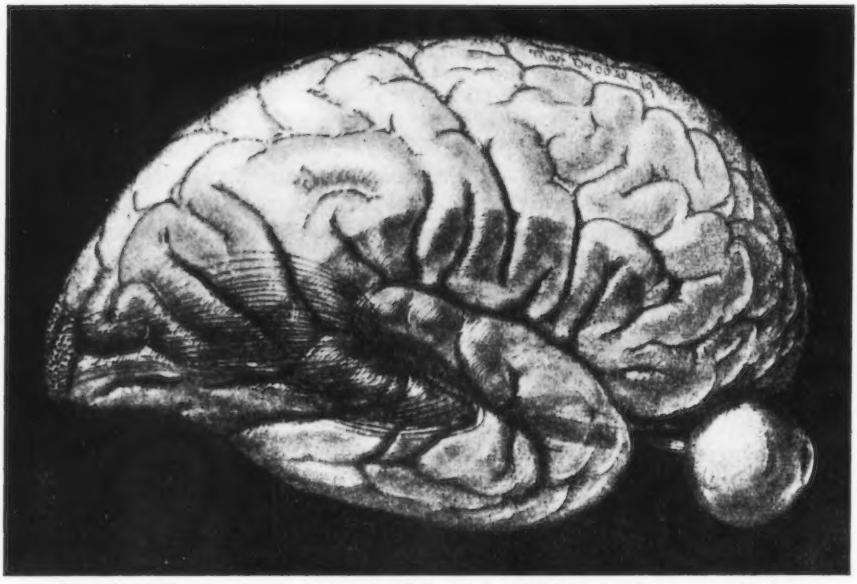


FIG. 11.—Diagram of the pathway of the optic radiation in the temporal lobe as proposed by Cushing (1922). It would seem that the fibres of the optic radiation do not extend as far forward in relation to the tip of the temporal horn as they appear to do in this diagram.

radiation capping the anterior pole of the temporal horn. Although what one must assume to be the optic radiation in the myelinogenetic studies of young infants may be seen to surround the temporal tip in Pfeiffer's (1925) illustrations (figs. 42, 43, 46). It seems quite possible this relationship may alter with postnatal development of the hemispheres. Meyer (1936) appeared to sustain this idea in reporting his anatomical material which "shows clearly that the most anterior bundle does not go around but along the side close to the anterior end of the pole [of the temporal horn]." The general outline of the visual radiation may be gained by gross dissection (Martin, 1937; Rasmussen, 1943) and although this work tends to support Meyer's statements, in the hands of the present author, at least, the identification of optic radiation and particularly a precise differentiation between radiation and frontal and anterior commissure fibres sweeping into the temporal lobe through the temporal stem tends to be somewhat arbitrary. The most convincing demonstration of the anterior extremity

XUM

of the temporal portion of the optic radiation has been shown in the generally neglected paper of Probst (1906). He had the good fortune to obtain a brain with a discrete vascular injury to the lateral geniculate body, and using the Marchi method could readily define the extent of the radiation. Fig. 12 from his article shows the position of the most anterior

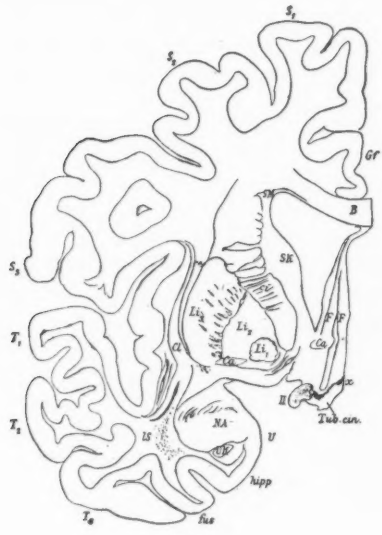


Fig. 3.

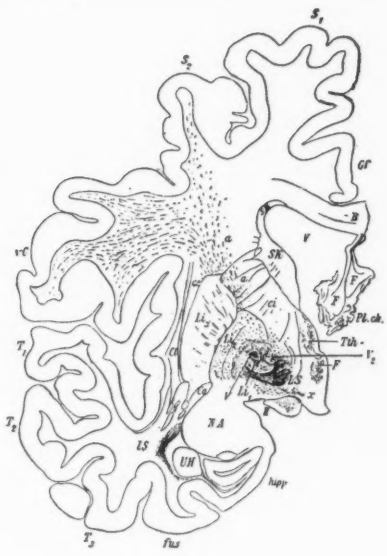


Fig. 4.

FIG. 12.—The relationship between the tip of the temporal horn and the anterior portion of the detour of the optic radiation in the temporal lobe as found by Marchi studies following a vascular lesion in the external geniculate body (Probst, 1906).

fibres in the optic radiation lying lateral to the tip of the temporal horn and amygdala. The distance between the radiation and the anterior extremity of the temporal horn may be noted.

This relationship between the tip of the temporal horn and the optic radiation apparently explains the finding in Fox and German's case (1935) and in our own material that the temporal horn may be surgically opened without the production of a defect of the visual field. The wide openings made into the temporal horn in patients Mu and Jo suggests either that the results are due to individual anatomical variation or that our present testing methods remain too insensitive.

With regard to the functional architecture, i.e. the precise correlation between discrete retina and radiation representation of the visual radiation in the human temporal lobe, there appears to be a complete lack of anatomical evidence.

XUM

(C) *An Hypothesis Regarding the Representation of Retinal Areas in the Temporal Lobe of Man*

As mentioned above, the present hypothesis must be based solely upon physiological evidence obtained by examination of the visual fields. It is based on our own material and on the assumption that the visual field changes are due to injury to the optic radiation alone. Although damage to the most proximal portions of the optic radiation can occur as in Case UN (fig. 3) with a radical postero-medial temporal removal, in the remainder of the cases presented no approach had been made to the lateral geniculate body. The retention of the medial pia-arachnoid in those instances where the mesial temporal structures were removed made injury to the optic tract or anterior choroidal artery unlikely, at least that it could have occurred in all of the 23 patients who showed incongruous defects of the visual fields.

In Cooper's (1956) experience with surgical obliteration of the anterior choroidal artery for Parkinsonism, visual field defects were infrequent and this suggests that the lateral geniculate body may be less dependent upon the vascular supply of the anterior choroidal artery than was formerly supposed.

A conception of an architectural arrangement which would fulfil the requirements both of the direction from which surgical ablation of the

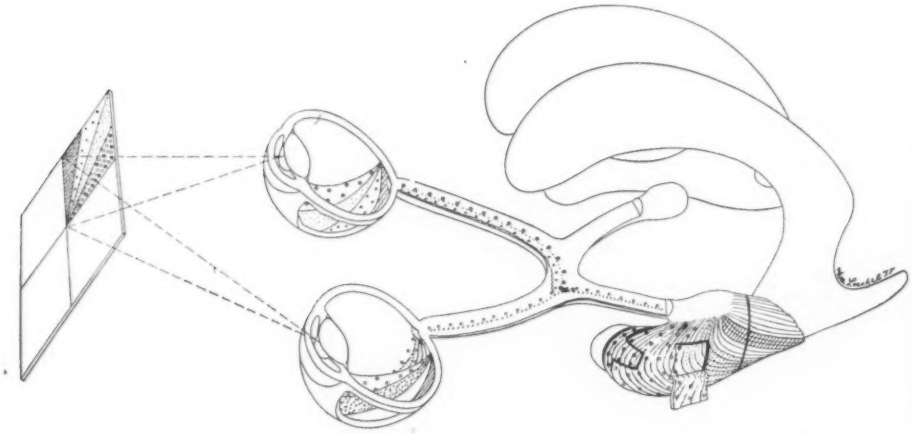


FIG. 13.—An anatomical hypothesis regarding the representation of the retinal inferior quadrants in the temporal portion of the optic radiation in man based upon the present study of visual field defects following temporal lobectomy. Note that the tip of the temporal horn is not capped by the radiation and although the distribution from each retina extends anteriorly to an equal degree, the representation from the homolateral retina lies lateral to that from the contralateral retina. The macular fibres at all levels are considered to lie mesial to the fibres representing the periphery of the retina.

XUM

optic radiation could proceed and the resulting defects of the visual fields is shown in fig. 13. Features to be noted as follows:

(1) The radiation does not cap the temporal horn.

(2) The representation of the retina on either side of the vertical meridian lies farthest forward in the radiation and therefore makes the largest excursion in the temporal lobe.

(3) A lesion of the most anterior portion of the anterior looping fibres would account for the para-vertical defects of fig. 9. As the lesion extended posteriorly and inferiorly the inferior border of the visual field defect would change its angle from an oblique to a horizontal direction from the fixation point.

(4) A lesion advancing from the lateral aspect of the radiation would injure the ipsilateral retinal fibres more than the contralateral, resulting in incongruous defects larger on the side of the lesion.

(5) A lesion advancing from the anterior aspect of the radiation would injure ipsilateral and contralateral retinal fibres to an equal degree resulting in congruous defects.

Dr. Wilder Penfield's permission to include 6 of his cases is most deeply appreciated as is his criticism of the manuscript during preparation. Helpful discussion was also received from Drs. Theodore Rasmussen, Milton Shy, Ira Telford and Ludwig von Sallmann.

SUMMARY

The visual fields in 41 cases of temporal lobectomy for epilepsy have been studied for evidence regarding the fibre architecture of the anterior portion of the optic radiation. The evidence suggests that the visual field defects in these cases are the result of a lesion solely of the optic radiation. Visual field defects were found (1) not to affect visual acuity, (2) not to alter the size of the blind spot, (3) to have sloping inferior margins, (4) to pass over the horizontal meridian, (5) to have the density in the defect roughly proportional to the perpendicular distance from a line paralleling the inferior margin of the defect and passing through the fixation point, (6) to be both congruous and incongruous, but if incongruous, to have the larger defect of the visual field in the eye on the side of the lesion. In terms of a physiological-anatomical correlation these findings were explained respectively as follows: (1) one half of macular vision is sufficient to permit normal acuity, (2) alteration of one field of vision does not entail a change in the visual projection of the remaining intact retina, (3) the fibres from adjacent retinal elements are spatially separated in the optic radiation, (4) the representations of the upper and lower visual quadrants in the optic radiation are not separated by the macular fibres, (5) the macular representation lies medial to that of the peripheral retina, (6) in the anterior portions of the optic radiation the representation of the

XUM

ipsilateral and contralateral retinal halves both extend an equal distance anteriorly but the ipsilateral retinal representation lies lateral to the contralateral retinal representation.

REFERENCES

ABBIE, A. A. (1933) *J. Anat., Lond.*, **67,** 491.

ARCHAMBAULT, L. (1909) *Albany Med. Ann.*, **30,** 118.

ASK-UPMARK, E. (1932) *Acta ophthal., Kbh.*, **10,** 271.

BENDER, M. B., and STRAUSS, I. (1937) *Arch. Ophthal., N.Y.*, **17,** 765.

COOPER, I. S. (1956) Personal Communication.

CUSHING, H. (1922) *Brain*, **44,** 341.

——, and WALKER, C. B. (1915) *Brain*, **37,** 341.

FOX, J. C., Jr., and GERMAN, W. J. (1935) *Arch. Neurol. Psychiat., Chicago*, **33,** 791.

GLOBUS, J. H., and SILVERSTONE, S. M. (1935) *Arch. Ophthal., N.Y.*, **14,** 325.

GUNKEL, R. D., and RYAN, R. W. (1955) *Amer. J. Ophthal.*, **40,** 897.

HALSTEAD, W. C., WALKER, A. E., and BUCY, P. C. (1940) *Arch. Ophthal., N.Y.*, **24,** 948.

HARRINGTON, D. O. (1939) *Arch. Ophthal., N.Y.*, **21,** 453.

HARRIS, W. (1897) *Brain*, **20,** 308.

HOLMES, G. (1918) *Brit. J. Ophthal.*, **2,** 352.

—— (1952) "Introduction to Clinical Neurology," 2nd edition. Edinburgh.

——, and LISTER, W. T. (1916) *Brain*, **39,** 34.

HORRAX, G., and PUTNAM, T. J. (1932) *Brain*, **55,** 499.

LILLIE, W. I. (1925) *Amer. med. Ass.*, **85,** 1465.

MACKENZIE, I., MEIGHAN, S., and POLLOCK, E. N. (1933) *Trans. ophthal. Soc. U.K.*, **53,** 142.

MARTIN, J. P. (1937) *Trans. ophthal. Soc. U.K.*, **57** (Pt. I), 141.

MCCONNELL, A. A. (1933) *Brit. med. J.*, **2,** 226.

MEYER, A. (1907) Trans. Ass. Amer. Phycns., **22,** 7.

—— (1936) *Arch. Neurol. Psychiat., Chicago*, **35,** 823.

OLDBERG, S. (1937) *Acta med. scand.*, **93,** 330.

PENFIELD, W. (1940) *Arch. Ophthal., N.Y.*, **24,** 962.

PFEIFFER, R. A. (1925) Myelogenetisch-Anatomische Untersuchungen über den zentralen Abschnitt der Schleitung. Berlin.

PROBST, M. (1906) *S. B. Akad. Wiss. Wien.*, **115,** 103.

PUTNAM, T. J. (1926*a*) *Arch. Neurol. Psychiat., Chicago*, **16,** 566.

—— (1926*b*) *Arch. Neruol. Psychiat., Chicago*, **16,** 683.

RASMUSSEN, A. T. (1943) *Anat. Rec.*, **85,** 277.

RIDDOCH, G. (1917) *Brain*, **40,** 15.

RONNE, H. (1915) *Klin. Mbl. Augenheilk.*, **54,** 399.

—— (1919) *Klin. Mbl. Augenheilk.*, **63,** 358.

—— (1927) *J. Amer. med. Ass.*, **89,** 1860.

SANFORD, H. S., and BAIR, H. L. (1939) *Arch. Neurol. Psychiat., Chicago.*, **42,** 21.

SCHIRMER, O. (1912) *Arch. Ophthal., N.Y.*, **41,** 136.

SPALDING, J. M. K. (1952) *J. Neurol. Neurosurg. Psychiat.*, **15,** 99.

TRAQUAIR, H. M. (1922) *Brit. J. Ophthal.*, **6,** 251.

—— (1933) *Brit. med. J.*, **2,** 229.

—— (1949) An Introduction to Clinical Perimetry. 6th edition. St. Louis.

PRIMARY TUMOURS OF THE THALAMUS

BY

WYLIE McKISSOCK AND KENNETH W. E. PAINE

(From the National Hospital, Queen Square, and St. George's Hospital, London)

TUMOURS of the thalamus would have little surgical interest, being intracerebral in situation and so not amenable to any direct surgical approach, were it not that these tumours are often slowly-growing and that some palliative procedure might enable the patient to survive a number of years. The clinical diagnosis of these tumours, although not usually reliable enough for operative intervention, can often be made when one is aware of the symptoms and signs peculiar to space-occupying lesions in this site—signs and symptoms, all of which have not hitherto been attributed to thalamic neoplasms.

We propose to report 24 cases of thalamic tumour, diagnosed by ventriculography, and some confirmed by post-mortem examination, and to consider their mode of presentation, method of investigation, pathology and treatment. The term "thalamic tumour" must not be too restricted, for there is no doubt that a neoplasm which starts in the thalamus will spread to adjacent structures—the internal capsule and basal ganglia on the same side and to the thalamus on the other side—in the course of time. The patients we include are those in whom the tumour is believed to have originated in the thalamus, and is involving mainly the thalamus, albeit by the time the patient comes into the hospital there may be spread to these neighbouring structures.

INCIDENCE OF THALAMIC TUMOURS

Over one hundred cases of thalamic tumour have been reported, most of them because of some peculiar clinical feature which was present. The literature does not therefore, give a true picture of the incidence of these tumours which must be more common than these reports would suggest. Bramwell (1899) reports 4 patients with tumours of the thalamus although only 1 was mainly thalamic, in a series of 122 brain tumours—an incidence of 1 per cent. Golla (1931) found the basal ganglia involved by tumour in 9 patients out of 55, but one is not able to say in how many of these the thalamus was implicated. Elvidge, Penfield and Cone (1937) in a pathological study of 210 cases of cerebral glioma found that in only 2 were the basal ganglia involved, in both cases by an astrocytoma, but

again we cannot tell to what extent, if at all, the thalamus was invaded. The present series of 24 patients with tumours of the thalamus occurred in patients admitted to the National Hospital, Queen Square, London, or the Atkinson Morley Hospital, Wimbledon, under the care of one of us (W. McK) during a period when approximately 2,500 patients with brain tumours were seen. In our experience, therefore, about 1 per cent of cerebral tumours are primarily thalamic.

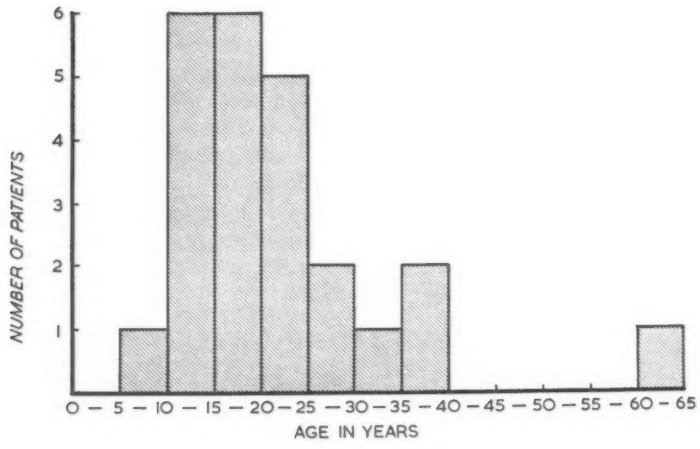
Clinical Picture

Age of Patient on Admission to Hospital

The age of the patients varied from 6½ to 61 years at the time of admission to hospital. Only one was over 38 years of age. 17 patients were between the ages of 10 and 25 years and the mean age was just under 20 years (Table I).

TABLE I

AGE OF PATIENT ON ADMISSION

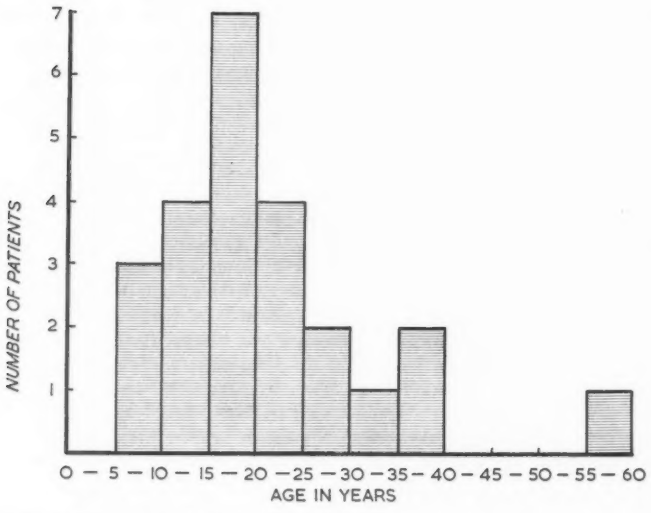


Age at Onset of Symptoms

This age would appear to be of more value than the age at the time of admission as it approximates more closely to the time of onset of the tumour. It does at least represent the first indication that the tumour is affecting the host. The age at onset varied from 6 to 60 years again with the mean of just under 20 years. Three-quarters of the patients dated their first symptom before the age of 25 years (Table II).

TABLE II

AGE AT ONSET OF SYMPTOMS

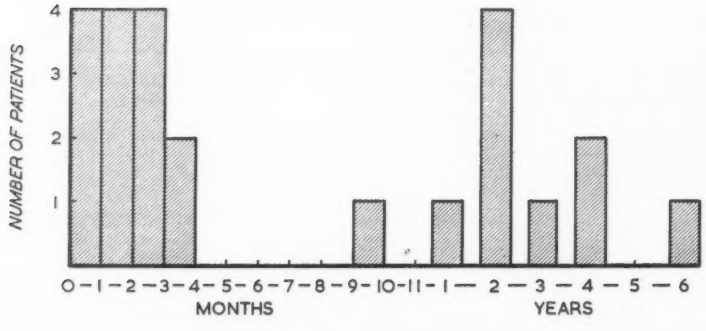


Duration of Symptoms before Admission

From the previous statements it would seem that the duration of symptoms before admission was usually short and it varied from less than a month to as long as six years (Table III). Over half of the patients (14)

TABLE III

DURATION OF SYMPTOMS



XUM

had had symptoms for less than four months before seeking relief. 8 had had symptoms for more than a year. The symptoms which heralded the illness did not appear to bear any relation to the duration of symptoms before admission.

With regard to the histology of the tumour in relation to the duration of symptoms only seven reports were available. 2 patients with symptoms for less than a year had a spongioblastoma multiforme and two had astrocytomas. 2 patients with symptoms for more than a year had a spongioblastoma and one a ganglioneuroma. It would seem that the duration of symptoms at the time of admission was no indication as to the nature of the tumour.

Sex

11 of the patients were males and 13 females. The mean age of onset of symptoms in the males was $17\frac{1}{2}$ years and in females 22 years. There were 3 males but no females whose symptoms began before the age of 10 years.

TABLE IV

INITIAL SYMPTOMS

			NO. PATIENTS
RAISED INTRACRANIAL PRESSURE	HEADACHE	16	16
	VOMITING	7	
	APATHY	3	
	ANOREXIA	1	
HEMIANOPIA		1	1
DIPLOPIA		4	
MOTOR DISTURBANCE	WEAKNESS	3	5
	SHAKINESS	3	
SENSORY SYMPTOMS			1
EPILEPSY			1

Symptoms and Signs

Initial symptoms (Table IV).—In 16 patients headache was the initial symptom and in 7 was associated with vomiting, 2 of whom had noticed a lack of initiative as well. One of the 16 had noticed drooping of the eyelids and lack of initiative in addition to the headache, and another had anorexia as well as headache.

Diplopia was an initial complaint in 4 patients, 3 of whom had headaches also, but in the other one the diplopia alone was the first complaint.

XUM

Weakness of a limb or of the two limbs on the same side of the body was the first symptom in 3 patients 1 of whom had tremors in the affected limbs and another had noticed numbness and hyperæsthesia of the involved members. None of these patients had headache early in their illness.

Tremors of one or more limbs occurred in 3 patients as the first evidence of their tumour, in 2 cases without weakness. None of these patients complained early of headaches.

The onset of 1 patient was manifest by a focal sensory attack and in another by loss of vision in one half homonymous field.

Symptoms and signs at the time of admission are best considered in groups: (1) Those due to raised intracranial pressure. (2) Disturbance of motor function. (3) Alteration of sensory perception. (4) Visual field defects. (5) Ocular signs. (6) Auditory signs and symptoms. (7) Endocrine disturbances. (8) Epilepsy. (9) Psychosis. (10) Miscellaneous signs and symptoms. (Tables V and VI.)

(1) *Raised Intracranial Pressure*

Headache, vomiting and papillœdema were the commonest of the symptoms and signs in these patients. 23 of the 24 patients had at least

TABLE V

ALL SYMPTOMS

			NO. PATIENTS
RAISED INTRACRANIAL PRESSURE	HEADACHE	22	23
	NAUSEA AND VOMITING	16	
	APATHY AND DULLING OF INTELLECT	13	
	DIPLOPIA	3	
	VISUAL FAILURE	10	
	LARGE HEAD	1	
MOTOR DISTURBANCE	WEAKNESS	5	9
	SHAKING OF LIMBS	4	
BRAIN STEM SYMPTOMS	GIDDINESS	4	4
SENSORY DISTURBANCE			2
VISUAL FIELD DEFECT			1
AUDITORY SYMPTOMS			3
ENDOCRINE DISTURBANCE	MENSTRUAL DISORDERS	2	4
	OBESITY	3	
	VORACIOUS APPETITE	1	
EPILEPSY			8
PSYCHOSIS			2

XUM

TABLE VI

CLINICAL SIGNS

		NO. PATIENTS
RAISED INTRACRANIAL PRESSURE	PAPILLOEDEMA 18 APATHY AND DULLING OF INTELLECT 14 EXTERNAL RECTUS PALSY 3 VISUAL FAILURE 5 LARGE HEAD 1	22
OPTIC ATROPHY		2
HEMIANOPIA		4
MOTOR DISTURBANCE	HEMIPARESIS 11 TREMOR OF LIMBS 8	16
CEREBELLAR SIGNS	NYSTAGMUS 12 TILTING OF HEAD 2	13
SENSORY SIGNS	IMPAIRMENT OF SENSATION 5 DISTORTION OF SENSATION 2	5
OCULAR SIGNS	UNEQUAL PUPILS 6 ABNORMAL PUPILLARY REACTIONS 6 IMPAIRED CONJ. DEV. 3 3RD. NERVE PALSY 4	13
APHASIA		2
PSYCHOSIS		3

one of the above triad. Headaches were present in 22: their character varied, but a number of types were described. The situation was variously, frontal, bitemporal or occipital, occasionally spreading from the neck to the top of the head and sometimes stated to be "all over." The headache in some patients was only mild, and had been present for a few weeks or a number of months. In others the headache was of increasing intensity over a period of months or sometimes days. Some patients had had intermittent headaches, coming on suddenly and lasting perhaps for a few days before passing, and leaving the patient free from symptoms for days or weeks before the onset of another. One of these attacks may have been the immediate reason for the patient's admission to hospital.

Nausea and vomiting were present in 16 of the patients and in each the sickness was related to the headaches.

XUM

Papillœdema confirmed the presence of raised intracranial pressure in 18 of the patients and in all but 2 was of moderate or severe degree. Only 1 patient with papillœdema had never complained of headache. Of the 5 patients who had headaches but not papillœdema, normal fundi were present in 4 and optic atrophy in 1. The vision of this last patient was 6/12 in each eye, suggesting that the atrophy was probably primary rather than consecutive.

Patients with severe increases of intracranial pressure tend to become apathetic with dulling of the intellect, and later drowsy with progression to coma. The patients or relatives of 13 of the patients in this series had noticed one or more of these changes. In 10 cases examination confirmed the history and showed that these changes could be related to the raised intracranial pressure. The 3 patients with a history of mental dulling, but in whom examination failed to confirm the history were considered in detail. One young man thought that his powers of concentration were not as good as formerly, and he had become disinterested in his work (changes which were noticed over a period of at least two months) yet this patient had passed for his degree of Bachelor of Arts only one month before admission. His presumably high premorbid intelligence had not deteriorated sufficiently to be detectable by routine clinical tests. One boy's parents had noticed a decline in their child's mental ability over a period of years. Clinically he could not be faulted with simple tests of mental function, but again his normal intelligence may have been high. The third, a girl of 12 years, was said to have been drowsy and inactive for two months but at the time of examination she was alert, and superficially of average intelligence. Perhaps she had passed into a compensatory phase of her increasing intracranial hypertension.

There were 4 patients whose examination disclosed mental deterioration, which could have been due to the effects of raised intracranial pressure, yet there had been no history suggesting any such mental change. One man deteriorated rapidly after a lumbar puncture at another hospital, and when admitted to the neurosurgical unit was drowsy, whereas two days earlier he had been alert. In a second patient the changes recorded on examination were only slight impairment of memory and "slow cerebration." In a third, deterioration followed a pyrexial illness so that in two days the patient became drowsy and disinterested. The final patient, a student, was drowsy when examined and it is likely that a history of increasing apathy might have been obtained but for some language difficulty.

The mental changes were variously described but were the type of change encountered in any patient with raised intracranial pressure and were not necessarily specific for patients with thalamic tumours.

Double vision due to a unilateral or bilateral sixth nerve palsy was complained of by 3 patients. Examination disclosed a sixth nerve palsy

XUM

in one other patient, who had not complained of diplopia, probably because of the severe reduction of his visual acuity by papillœdema. At the time of examination the visual acuity was reduced to appreciation of hand movements.

Visual failure was a complaint of 10 patients. 4 had noticed a progressive deterioration of their eyesight, and in these examination confirmed the visual loss. 3 patients had had attacks of blurring vision, or even blindness, in association with severe headaches. 2 of the 3 patients had an acuity of better than 6/12 at the time of examination. The third had 6/6 vision in one eye but only 3/60 in the other. In 1 patient the visual difficulty was described as "woolly patches" in front of the eyes. On examination he had moderate papillœdema but a visual acuity of 6/6 in each eye. In 1 patient with a near vision of J2, J4, the blurring of eyesight was only noticeable when she was looking at distant objects. No patient without complaint of visual impairment was found on examination to have deterioration of visual acuity.

A large head, in a boy of 11, was commented upon by his parents. This boy had a severe hydrocephalus and gave a history dating from the age of 8 years. No other patient had an enlargement of the head.

(2) *Disturbance of Motor Function*

5 patients complained of weakness of one or more limbs, and in all the weakness was progressive, and occurred in the arm and leg on the side opposite to that of the thalamic tumour. The progression of the hemiparesis occurred during a period which varied from four weeks to eighteen months. Examination revealed a slight hemiparesis in 3, 1 with a slight sensory loss and another with a severe sensory loss in the involved limbs. The fourth patient had a moderate hemiplegia and the fifth a severe hemiplegia both with profound sensory loss as well. The last 4 patients had a typical pyramidal weakness with increased tone and tendon reflexes and an extensor plantar response.

In addition to these 5 patients, there were 6 others with a hemiparesis detected on examination although the patient had made no spontaneous complaint of weakness. In some cases this was because the disability was so mild, and in others because the hemiplegia had developed rapidly in the few days before admission, when the patient was becoming drowsy or confused from the effects of intracranial hypertension. In 4 cases the hemiplegia was slight, with increased tone and tendon reflexes and diminished abdominal reflexes on the same side. 3 patients had an extensor plantar response in addition. In these the sensory perception of the hemiplegic limbs was normal, but in the fourth there was slight sensory impairment. In the other 2 cases the hemiplegia was moderately severe with spasticity and an extensor plantar response. In both, sensation was regarded as normal but one was drowsy and co-operation was not adequate for full testing.

XUM

Disturbance of motor function may also be manifest in tremors when the extrapyramidal or cerebellar pathways are involved. 4 patients had complained of shakiness of one or more limbs and tremors were found on examination in 8 patients. In 2 instances it was a terminal tremor on volitional movement in patients with hemiparesis. 2 other patients had tremor of the outstretched hands, which was increased on the finger-nose test. One of these had other "cerebellar" signs in the same arm and leg. A fifth patient appeared to have a mixture of hemiparesis and "cerebellar" signs in the same side, and a tremor when performing the finger-nose test. Another, with a small tumour projecting into his third ventricle causing a severe hydrocephalus, had bilateral tremor at rest and on movement. The seventh patient had a terminal tremor on movement of the arm, but no other abnormal signs in that arm, and the final one, with a hemiparesis and severe position-sense loss, had a severe tremor on movement.

Of these 8 patients only 1 was found to have a tumour spreading down the brain-stem. 5 had large tumours which were almost certainly invading the internal capsule and basal ganglia. One had a moderate-sized tumour with a severe hydrocephalus of the lateral ventricles and the last had a small tumour occluding the third ventricle and causing gross dilatation of the lateral ventricles (fig. 1, Plate I). The hydrocephalus of the first 6 patients was moderate in 5 and slight in 1.

6 patients had an abnormal gait in all cases related to the motor disturbance of their legs.

(3) *Sensory Disturbances*

Only 2 patients complained spontaneously of sensory disturbances. One had experienced focal sensory attacks ultimately succeeded by "an increased sensitivity of the skin of the left side of the face" and "combing of the hair had produced a sensation as though a rake was being drawn across the head." The other had noticed increasing numbness of one hand for four weeks, and "the arm had become dead like jelly."

Neurological examination revealed sensory impairment in 5 patients, including the 2 above. It is unfortunate that the sensory examination is not complete in all cases because of lack of co-operation of the patient. All 5 patients with sensory loss had a hemiparesis and 2 of them had a hemianopia. The modalities of sensation involved varied in the 5 cases and are tabulated in Table VII. Post-mortem examination in 2 patients showed that the tumour had spread to the posterior limb of the internal capsule. In 2 others the ventriculogram demonstrated a large tumour spreading laterally probably into the internal capsule and in the fifth patient the presence of cranial nerve signs suggested that the tumour had spread into the mid-brain.

Distorted sensations were encountered in 2 patients but in none was a complaint of spontaneous pain elicited. One patient had noticed the

XUM

TABLE VII

SENSORY LOSS

PATIENT	LIGHT TOUCH	PIN PRICK	TWO POINT DISCRIMIN.	POSITION SENSE	STEREOGNOSIS	VIBRATION SENSE
1	0	0	X			
2	XXX	XXX	XXX	XXX	XXX	
3	0	XX	X	XXX	XX	XX
4		X	X			
5	XXX	XX		XX		XXX

distorted sensations herself when combing her hair, and on examination there was an unpleasant reaction to heavy stroking stimuli on the affected side. Cotton-wool, for example, felt like sandpaper. The other patient complained of the distorted nature of pin-prick sensation. The prick was poorly localized, appeared to be spread over a large area, was most unpleasant and associated with a delayed reaction time. The unaffected limbs did not show any of these features so that although the patient was drowsy, there was no doubt of the altered character on the affected side.

(4) *Visual Field Defects*

Visual failure and diplopia have been considered previously and the only other visual symptom was that of an hemianopic field defect. This patient had noticed difficulty in seeing to the left side, and a homonymous hemianopia was demonstrated on examination. Bilateral optic atrophy was present but the visual acuity was 6/5 in each eye.

(5) *Ocular Signs* (Table VIII)

A variety of ocular signs, singly or in combinations, were encountered in 19 of the patients.

Nystagmus was present in 12, in 5 of whom it was to the right or left, and in none of whom were other "cerebellar" signs found. In 4 of these patients the nystagmus was to the side of the thalamic tumour but in the fifth was to the opposite side. 3 patients had nystagmus when looking to either side and 2 of these had other signs of "cerebellar" disturbance. In all 3 cases the tumour was on the left. 2 patients had nystagmus to the left and on looking upwards, and one of these had other signs of "cere-

TABLE VIII

CASE NUMBER	NYSTAGMUS	UNEQUAL PUPILS	ABNORMAL PUPILLARY REACTIONS	IMPAIRED CONJUGATE DEVIATION	THIRD NERVE PALSY
1		X	X	X	X
2					X
3	X				
4		X	X	X	
5			X		
6		X			
7	X	X			
8	X				
9			X		
10	X		X		
11	X				
12		X			
14	X				
15	X				X
17	X				
18				X	?
19	X				
20	X		X		
24	X	X			

bellar" dysfunction. Both had left-sided tumours. One patient had nystagmus on looking to the right, upwards or downwards in association with other "cerebellar signs," and the tumour lay on the right side. The final patient had nystagmus on looking to either side and on looking upwards: other "cerebellar" signs were present and the tumour was on the left. Thus in 7 patients the nystagmus was to the same side as the tumour but in only 1 to the opposite side.

Inequality of the pupils occurred in 6 patients. In 3 instances there was no other abnormality of eye movements or reactions, and in all instances the smaller pupil was on the side of the tumour. In 1 patient the tumour had spread down the brain-stem at least to the level of the red nucleus, but in the second an extensive tumour invading the internal capsule an the basal ganglia did not spread downward into the mid-brain. In the third, most of the tumour was removed at operation, and the remnants found at post-mortem were limited to the thalamus.

XUM

Poor pupillary reactions were found in 6 patients. In 3 the light reaction on accommodation was brisk. In one of these the changes were due to severe reduction of visual acuity by the papillœdema, but this was not the cause in the others. One patient had neither reaction to light nor on accommodation, another had sluggish reactions both to light and convergence and the final patient had normal reactions to light but no reaction on convergence.

Impairment of conjugate movements of the eyes were found in 3 patients, in 2 of whom only upward movement was lost and in the third both upward and downward movements were absent.

A unilateral third nerve palsy was present in 4 patients, but in none was complete and the assumption that it was a cranial nerve lesion may have been incorrect.

Sixth nerve palsies have been mentioned earlier and in no instance could there be any certainty that these were due to direct effects rather than the indirect effects of raised intracranial pressure.

Of the 13 patients with ocular signs, excluding nystagmus, post-mortem examination or inference from ventriculography showed that the tumour spread down the brain-stem in 7. In 3 only was it quite certain that there was no macroscopic spread to the mid-brain. In the remaining 3 the tumour was large, and may well have spread along the aqueduct into the mid-brain.

(6) *Auditory Signs and Symptoms*

3 patients complained of tinnitus and one of deafness as well. The latter had noticed hissing noises in the deaf ear for a month prior to admission, and examination disclosed deafness of auditory nerve origin. The tumour lay on the same side as the deafness. The second patient with buzzing in the right ear, had a tumour in the right thalamus, as also had the third, who complained of noises in both ears. Neither of these 2 patients showed any change in hearing or vestibular functions on either side.

(7) *Endocrine Disturbances*

Menstrual disturbances were encountered in 2 patients. One young girl who had been menstruating for a year had observed an increased intermenstrual period for the six months prior to admission: her other symptoms began after this change had occurred. The second patient had noted amenorrhœa for three months before her admission to hospital.

3 patients had noticed an increase in weight and whilst 1 also had menstrual disturbance, the other 2 had not. These patients were aged 12, 17 and 20 years, and all were described as plump, but with well-developed secondary sexual characters and no hirsutism.

One other patient was underdeveloped at the time of his admission at the age of 14 years.

XUM

A complaint of voracious appetite was volunteered by 1 patient who was one of the 3 who were obese.

(8) *Epilepsy*

8 patients experienced attacks which might have been epileptic in nature. 3 had had attacks of numbness which were undoubtedly focal sensory seizures. In 1 unconsciousness supervened and in another dysphasia was present during the attacks. One patient had had a "fit" in a previous hospital but there was no record of its character. Another had had "spasms" around the eye and mouth and yet another had had one attack of abnormal sensation of smell which was probably an olfactory aura. "*Déja vu*" phenomena constituted the attacks of another patient and the final one complained of repeated "curious abdominal sensations." In the cases in which a post-mortem was obtained, the tumours were not invading the cortex.

(9) *Psychiatric Disorders*

The mental changes associated with raised intracranial pressure have been mentioned previously but there were 3 patients with changes not attributed to this cause. One had been in Mental Hospitals on three occasions before admission and a diagnosis of paranoid schizophrenia had been made. He received treatment by E.C.T. and insulin coma, and there was no doubt that his mental behaviour justified the diagnosis. When seen by us he was drowsy and apathetic due to raised intracranial pressure. He had a tumour of the right optic thalamus probably growing into the brain-stem but, as he is still living, we have no pathological confirmation.

A boy of 11 years was said to have been unhappy at school and to have played truant on a number of occasions as well as having stolen money. He had been taken to court a year before his admission and had been placed on probation. There was no overt mental disorder on examination.

Examination disclosed mental changes in a third patient, a man of 61 who had a mild dementia and intellectual impairment: he was slightly hypertensive (155/95) and had a right thalamic tumour.

(10) *Miscellaneous Signs and Symptoms*

4 patients complained of giddiness, a symptom not infrequently associated with brain-stem lesions. One had noticed giddiness at night only and another who was disorientated and confused, complained of unsteadiness on rapid rotation of the head. The third patient had had occasional unsteadiness of gait associated with giddiness, and she had a severe hemiplegia, hemianæsthesia and hemianopia, but no disturbance of "cerebellar" function. The final patient had suffered attacks of a sense of rotation—the room around her felt as though it were turning—at the time when she had had severe headaches.

Tilting of the head was disclosed on examination in 2 patients. In 1

XUM

the head was turned to the right and he had a severe weakness of the left trapezius and of the left arm and leg. His bilateral tumour extended down the brain-stem. In the other patient the head was tilted to the left, and he had bilateral "cerebellar" signs, more on the right side than the left. Post-mortem examination revealed only a small tumour projecting into the third ventricle, with a severe hydrocephalus of the lateral ventricles but no spread of the tumour down the brain-stem (fig. 1).

Aphasia was present in 2 patients, both of whom had a left-sided tumour spreading into the temporal and frontal regions of the hemisphere.

Pathology

Unfortunately we have been able to make histological diagnosis of the type of tumour in only 7 patients. In 4 the tumour was classified as a spongioblastoma, in 2 as an astrocytoma and in the last as a ganglioneuroma (fig. 2).

Some were limited to a nodule in the third ventricle (fig. 1) and some to the thalamus, whilst others spread to adjacent structures in the hemisphere and brain-stem. In addition it had been noticed that the tumour might spread along the ventricular wall, as does the so-called subependymal glioma (fig. 4). In this way it can also spread down the brain-stem around the aqueduct. Involvement of the second thalamus via the massa intermedia or the floor or roof of the third ventricle was also a frequent occurrence in the late stages of the illness (fig. 8).

It is of interest to compare the size of the tumour in the patients with motor involvement with the size in those patients without motor disturbances. This can be assessed either from the ventriculographic picture, or in some cases from the post-mortem examination. Of the 11 patients with hemiplegia the internal capsule was involved by tumour in 5. In 3 instances the ventriculogram showed that the tumour was unquestionably large but in the remaining 3, although the actual size of the tumour is not known, it was certainly not small as evidenced by the air studies. Of the patients without hemiplegia 3 had tumours involving the internal capsule. In 5 the tumour was undoubtedly large, but in 2 it was small, one of these being shown at post-mortem as mainly a nodule projecting into the third ventricle (fig. 1). One patient had a tumour of uncertain size, though not a small one. One case has been excluded, a woman, who had no hemiplegia when first seen, but at her death three years later post-mortem showed that the tumour involved both thalami, one internal capsule and had spread subependymally around the ventricles (fig. 4). The patient had developed a hemiplegia some months before death.

Investigations

In all patients ventriculography was performed. Hydrocephalus was present in 22, and in 2 was restricted to the ventricle opposite to

the tumour, the ipsilateral ventricle being occluded by tumour. In 1 the hydrocephalus affected the ventricle on the side of the tumour, where the foramen of Monro was obstructed, and it did not prove possible to pass the air from the lateral ventricle to the third ventricle. 2 patients did not have enlarged lateral ventricles but there were other indications of a thalamic tumour.

Probably the earliest deformities produced by a thalamic tumour are bowing and obstruction of the third ventricle. In 1 patient this was the only deformity of the ventricular system other than the hydrocephalus (fig. 5). In 6 patients the bowing was present without other change of the third ventricle. 5 patients had obliteration of the posterior portion of the third ventricle and 7 showed a combination of these two changes, although those with obstruction probably had deformity which did not appear in the air pictures owing to non-filling of the obstructed posterior part of the third ventricle. There were thus 18 ventriculograms which showed abnormalities of the third ventricle (fig. 6).

The characteristic features of enlargement of the thalamus, whether due to tumour or other cause, must be an opening out of the trigonal region of the lateral ventricle with elevation of the floor of the body, posterior displacement of the trigone and perhaps depression or outward displacement of the temporal horn. Although such changes may be present in all cases except those of the very smallest tumours, ventriculography may not demonstrate them all in every case. 22 patients showed one, or combination, of such defects (fig. 7); elevation of the floor of the body of the lateral ventricle alone in 5, posterior displacement of the trigone and elevation of the floor in 12 cases, a defect of the temporal horn in addition to these above features in 3 cases, and elevation of the floor of the body and displacement of the temporal horn outwards or downwards in 2 patients (fig. 8). Of the remaining 2 patients one had a small nodule projecting into the third ventricle, and there was obstruction of the foramen of Monro in the other.

Treatment

Operative treatment for thalamic tumours was originally undertaken by direct attack through a frontal craniotomy. The results were uniformly unsuccessful. Torkildsen (1948, 1947) attempted only to relieve the symptoms of raised intracranial pressure by by-passing the third ventricular obstruction by the operation of ventriculocisternostomy, and he described 4 cases with survivals of eight, four and two years in 3, 1 patient dying post-operatively.

In the present series a ventriculocisternostomy was considered the treatment of choice for those patients whose main symptoms were those of intracranial hypertension, and in addition a course of radiotherapy was given post-operatively. This operation was indicated only if the lateral

XUM

ventricles were enlarged and there was no obstruction at the foramen of Monro.

TABLE IX

SURVIVAL AFTER TREATMENT

FORM OF TREATMENT.	HOSPITAL DEATH	SURVIVAL IN YEARS								
		0-1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9
TORKILDSEN	1	3		1	2	1+		1+		1+
RADIOTHERAPY	1	1+1		2					1+	
CRANIOTOMY	2	1								
NO TREATMENT	3						1+			
TOTALS	7	6		3	2	1	1	1	1	1

ONE PATIENT NOT FOLLOWED-UP IS EXCLUDED

+INDICATES THAT THE PATIENT WAS STILL ALIVE AT TIME OF LAST FOLLOW-UP

Results of Treatment (Table IX)

4 patients were not operated upon nor did they have radiotherapy. 3 of these died shortly after ventriculography, whilst the fourth was alive five years after the diagnosis was made and eleven years after the onset of his symptoms.

2 patients were subjected to craniotomy and 1 of these died in the post-operative phase. The other died three months after operation and four months after the onset of his symptom, although given a course of radiotherapy. 1 patient died after a posterior fossa exploration at which it was found impossible to perform a Torkildsen's operation.

6 patients were given a course of radiotherapy as the only treatment. 1 died during therapy, 1 within a year and 2 between two and three years after the completion of their treatments. 1 is alive but mentally retarded eight years after diagnosis and onset of symptoms, unable to work except to assist her mother at home. The last patient is working five months after the completion of the course of radiotherapy and less than a year after the onset of symptoms.

11 patients were treated by a Torkildsen's operation, 1 of whom died post-operatively. 1 died five months after operation having had no course of radiotherapy and 1 is alive and working six years after operation, also without having received any radiotherapy. Another patient was discharged with the understanding that she was to receive a course of radiotherapy in her own country, but we have no follow up details of her post-operative course. Of the 7 patients who received a course of deep

X-ray after Torkildsen's operation, 5 have died at two months, four months, two and a half years, three years, and three and a half years after operation. 2 are alive and working four and a half and eight years after surgery.

In the series there were 6 deaths after investigation or operation, and 1 during a course of radiotherapy. There were 10 deaths after treatment at varying periods from one month to three and a half years. 2 are alive but not able to work and 4 are alive and working (Table X).

TABLE X

STATE OF PATIENTS AT LATEST FOLLOW UP

FORM OF TREATMENT	USEFUL LIFE	USELESS LIFE
TORKILDSEN	6	4 (1 OPERATIVE DEATH)
RADIOTHERAPY	2	4
CRANIOTOMY	0	3 (2 OPERATIVE DEATHS)
NO TREATMENT	0	4 (3 DEATHS AFTER INVESTIGATION)

ONE PATIENT NOT FOLLOWED-UP IS EXCLUDED

TABLE XI

SURVIVAL SINCE ONSET OF SYMPTOMS

	SURVIVAL IN YEARS										
FORM OF TREATMENT	0-1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9	11	
TORKILDSEN	3			3	1			1+	2+		
RADIOTHERAPY		2	1+1				1		1+		
CRANIOTOMY	3										
NO TREATMENT	1*	1*	1*							1+	
TOTALS	7	3	3	3	1		1	1	3	1	

ONE PATIENT NOT FOLLOWED-UP

+ PATIENT STILL ALIVE AT TIME OF FOLLOW-UP

* PATIENT DIED AFTER INVESTIGATION BEFORE INSTITUTION OF TREATMENT

XUM

The survivial of patients since the onset of their symptoms was less than one year in 7, one to two years in 3, two to three years in 3, three to four years in 3, four to five year in 1, six to seven years in 1, seven to eight years in 1, eight to nine years in 3, and eleven years in 1. The last 5 patients are still alive (Table XI).

Those patients who are living useful lives or who were able to live a useful life up to shortly before their death number 8 or approximately 30 per cent of the patients (Table X).

Discussion

The youth of the patient with a thalamic tumour is at once apparent. This may well have a bearing on the type of tumour which occurs in this region of the brain, for Penman and Smith (1954) have shown that the early age at onset of symptoms in patients with brain tumours suggests that the tumour is more likely to be an astrocytoma (astrocytoma Grades I, II) than a spongioblastoma (astrocytoma Grade III or IV). Our own pathological reports do not confirm this, but this is not surprising, since those patients with the more benign type of tumour survived for some time after treatment and are either still living or have died elsewhere, so that post-mortem reports are not available. Again, the report of Penman and Smith would suggest that a patient who survives for three or more years after the onset of symptoms of a cerebral glioma is more likely to harbour an astrocytoma than a spongioblastoma.

In the present series the commonest signs and symptoms are those referable to raised intracranial pressure; but there was 1 patient who never displayed such symptoms or signs. Of 43 patients with thalamic tumours described in the literature, 35 had signs or symptoms of intracranial hypertension. It is not surprising that this was a frequent feature in any group of patients with intracranial tumours some years ago but today the diagnosis of cerebral tumour is frequently made before the advent of the signs and symptoms of raised intracranial pressure so that we must assume that early obstruction of the third ventricle by the expanding thalamus is responsible.

The tumour produces obstruction of the cerebrospinal fluid pathways, causing hydrocephalus of the lateral ventricles and of the anterior part of the third ventricle, and later there will be distortion of the lateral ventricle with uplifting of the trigone on the side of the tumour. For this reason the initial symptoms will be those of obstructive hydrocephalus and only later those of focal cerebral dysfunction. The intermittent nature of the headaches sometimes associated with visual blurring or loss is a feature common to tumours obstructing the ventricular system and this type of headache was met in some patients of this present series.

Disturbance of motor function was the next commonest evidence of the presence of a thalamic tumour. Contralateral hemiplegia was present

in 11 patients in this series although it was an obvious disability in only 4. Sensory loss was a not uncommon accompaniment of such motor dysfunction. The hemiplegia was characteristic of that of an upper motor neurone lesion with spasticity and an extensor plantar response. Post-mortem examination on such patients who died whilst under our care revealed that the internal capsule was involved by tumour, and it seems likely that it is at this level that the corticospinal fibres are interrupted. We also found, however, that the tumour could involve the internal capsule without there being evidence of a hemiplegia. It is, of course, well known that an infiltrating tumour will not necessarily cause dysfunction of the tissues in which it is growing.

In this series it was noted that the patient's illness might begin with symptoms either of raised intracranial pressure or of pyramidal involvement, which suggests that it is the medially placed tumours which obstruct the third ventricle early, and the laterally placed tumours which invade the internal capsule before obstructing the ventricular system.

Of the cases in the literature, 25 had a hemiparesis at some stage of their illness and of these some also showed a sensory loss.

Other motor phenomena have been reported previously and also noted in this present series. Disturbances of co-ordination were encountered in 8 patients, in whom such inco-ordination appeared to be out of proportion to the motor weakness or sensory loss. In some instances it could be said to be "cerebellar" in type although that only meant that it might be associated with other signs of cerebellar dysfunction such as nystagmus, dysmetria, diminished reflexes and intention tremor. Only one of these patients had an obvious spread of the tumour into the brain-stem which may have interfered with the cerebellar connections. The other patients had smaller tumours which involved the basal ganglia, except one in whom the tumour was a small nodule projecting into the third ventricle and causing gross hydrocephalus.

Patients are reported in the literature in whom inco-ordination and tremor of a peculiar type was present (Clarke, 1898; Stanley, 1898; Brzezicki, 1929; Ody, 1932; Smyth and Stern, 1938; Hyndman and van Epps, 1939; Mettler *et al.*, 1947; Sciarra and Sprofkin, 1953; Pfeifer, 1910). In 7 instances the basal ganglia were involved by tumour, and in 1 there was spread to the brain-stem. In some instances the tremor was said to be "Parkinsonian," but this was not the case in any of the present series. Some cases could be said to be examples of what Collier describes as "dancing ataxia," and attributed by him to lesions of the thalamus. It is our own opinion that the inco-ordination and tremor are the result of a complex disturbance of the pyramidal and extrapyramidal motor systems and of the sensory afferents in the brain-stem and internal capsule. Ascending cerebellar fibres may also be disturbed by the larger tumours invading the mid-brain.

XUM

5 patients had sensory disturbances. It is surprising that there were not more, since the thalamus is a great relay station in the sensory pathway (Ody, 1932; Head and Holmes, 1911). The typical clinical picture of the "thalamic syndrome" (Dejerine, 1906) of vascular lesions is lacking in patients with tumours, and spontaneous pain is rare, though distortion of sensation did occur in 2 patients. The literature contains notes of 20 patients with sensory loss in the contralateral limbs, and there is also record of spontaneous pain in the patients of Clarke (1898), Smyth and Stern (1938) Hyndman and van Epps (1939). Distortion of sensation and the thalamic pain reaction were also recorded on a number of occasions in the above reports. All cases in the present series with sensory loss had a hemiplegia and in the cases reported in the literature 5 only of 20 did not have an associated hemiplegia. It seems likely therefore that the hemiplegia and sensory loss are an indication that the tumour has spread outside the confines of the thalamus to involve the internal capsule.

Hemianopia, which was encountered in 4 patients, could be due to the involvement of the optic pathways in the optic tract, geniculate body, corpora quadrigemina or optic radiation. 6 such cases are recorded in the literature, 3 by Smyth and Stern (1938) and 3 by Hyndman and van Epps (1939). It is feasible that a hemianopia could be caused by a tumour still limited to the thalamus, if one included the corpora quadrigemina and geniculate bodies as part of the thalamus. In the cases in this series, however, the tumour was not so limited and it is impossible to say whether or not the hemianopia was due to spread outside the thalamus to the optic radiation or to pressure on the optic tract. In those 3 patients with a hemiplegia and hemianopia it seems likely that the optic radiation was affected near the internal capsule.

Inequality of the pupils, impairment of eye movements singly or of conjugate movements could be due to a lesion involving the quadrigeminal plate and mid-brain. Such findings were encountered singly or in combinations in 11 patients. This particular group of signs we considered to be the most characteristic of thalamic tumours and when present in a patient who is not drowsy from intracranial hypertension suggests most strongly that the tumour lies in the thalamus and is spreading to the mid-brain. Not all thalamic tumours, however, will present with such signs. Other references to the presence of these eye signs in patients with thalamic tumour are those of Smyth and Stern (1938) and Kinnier Wilson (1955).

Endocrine disturbances are known to occur in patients who have tumours producing hydrocephalus of the lateral and third ventricles, and have been ascribed to hypothalamic disorders caused by the pressure on the wall of the third ventricle; certainly we do not believe that the thalamic tumours act directly in producing endocrine changes.

Epilepsy, when focal in nature, is usually attributed to a subcortical or cortical lesion, but in our cases which came to post-mortem we were

XUM

not able to demonstrate any cortical spread of the tumour. It may be that the fits can originate from the grey matter of the thalamus, or perhaps by interference with the vascular supply of the medial temporal lobe. Post-mortem examinations were obtained in only 2 of the 5 patients who suffered from epilepsy.

Mental changes in patients of the present series have in all cases except one been attributable to the effects of raised intracranial pressure and hydrocephalus. The exception was a man whose psychosis was severe and who had received treatment for schizophrenia at a number of mental hospitals. He is still living and is known to have had his tumour for about eleven years. We are thus averse to the view that mental changes are directly produced by thalamic tumours, which some authors (Pfeiffer, 1910) believe to occur in some cases of thalamic tumour.

Involvement of the medial geniculate body, the relay station of auditory sensations in the thalamus, is unlikely to cause change in hearing as there is bilateral representation at this level in the brain. The only patient with unilateral deafness was affected in the ear on the same side as the tumour, probably by indirect pressure on the eighth nerve, rather than involvement of the medial geniculate body.

Tinnitus was a symptom in only 3 patients, including the deaf one, and with this exception no vestibular or auditory tests were found to be abnormal.

There is thus unfolded the clinical picture of a patient with a thalamic tumour, who typically is around the age of 20 years, and complains of the symptoms of raised intracranial pressure, perhaps of the intermittent type suggesting a ventricular obstruction, for a period of less than four months before seeking relief. Examination confirms the presence of raised intracranial pressure and may in addition show a mild hemiparesis or sensory loss, and occasionally a hemianopia. If the patient is alert, impairment of ocular movements especially loss of conjugate deviation or abnormal pupillary reactions will suggest most strongly that the tumour lies in the thalamus and perhaps the mid-brain. Absence of cranial nerve palsies, until late, exclude a primary tumour of the upper brain-stem, and the presence of intracranial hypertension will also make a pontine glioma unlikely.

The pathological nature of the tumours of the thalamus is known in only a few cases of this series, but the progress of the patient often suggests that the tumour is not highly malignant. The lower grade astrocytoma is the most likely tumour to grow at such a rate that the whole natural history of the tumour will cover more than three years.

These tumours may invade the internal capsule, and basal ganglia, spread to the opposite thalamus via the massa intermedia or the roof or floor of the third ventricle (Torkildsen, 1947), or spread to the mid-brain. The invasion of these structures seems in many instances to follow

XUM

the ependymal lining of the C.S.F. pathways similar to the spread of "subependymal gliomas." This type of spread forwards and backwards along the lateral ventricle is well shown in one case (fig. 3 and 4).

Clinically this spread of the tumour is shown by the development of a contralateral hemiplegia and sensory loss, and as a terminal feature hemiplegia may develop on the second side as well, indicating spread across the mid-line to the opposite hemisphere. Interference with motor co-ordination occurs during this development and may be due to involvement or the basal ganglia or the mid-brain.

The clinical diagnosis is not usually sufficiently certain for treatment to be instituted, and we have described the changes encountered in the ventriculograms of our patients. McConnell and Childe (1937) Hyndman (1938 and 1939), Davidoff and Epstein (1950) describe these features as characteristic of thalamic tumours. They are features of space-occupying lesions, not necessarily primary neoplasms and we have met similar changes due to other expanding lesions and to angiomas of the thalamus, but in our experience hydrocephalus of the lateral ventricles does not occur in these latter patients. If air studies show the features of a thalamic tumour, but without hydrocephalus, an arteriogram is obligatory (fig. 9). The 3 patients whom we have seen with thalamic angiomas have all presented with intraventricular and subarachnoid hæmorrhage.

Our treatment of these patients has been outlined above but without having a proper control series it is not possible to be dogmatic as regards the value of a ventriculocisternostomy, but of the 9 patients who survived this operation and who have been followed up, 6 have lived for more than two years. Of the remaining patients 9 left hospital alive but only 3 of these have survived for more than two years. The methods inherent in the selection of patients for operation do not make the groups comparable but clinically, the improvement that may follow a short-circuit operation in a previously rapidly deteriorating patient is justification enough for its performance in suitable cases.

Summary

(1) The clinical picture of a group of 24 patients with tumours of the thalamus is outlined and an attempt made to explain the causation of the symptoms.

(2) The pathological nature of the tumours, as far as information is available, is given.

(3) The characteristic ventriculographic appearances of thalamic tumours are described and illustrated.

(4) A rational method of palliative treatment by ventriculocisternostomy is advised.

(5) The results of such treatment are given and compared with other forms of therapy.

XUM

XUM

XUM

PLATE I

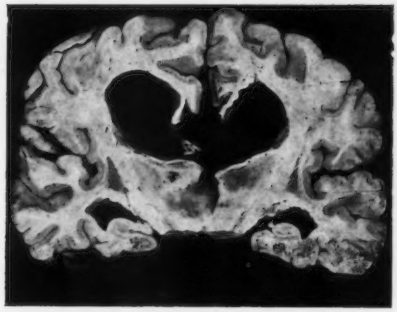


FIG. 1.—Coronal section of the brain to show the tumour of the left thalamus which consists mainly of a nodule projecting into the third ventricle causing an obstructive hydrocephalus (Case 10).

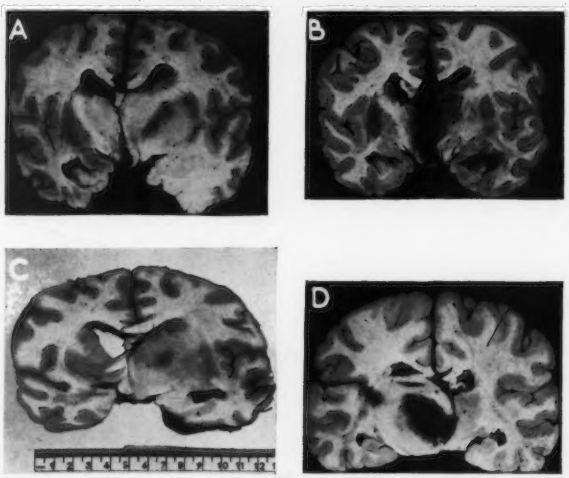


FIG. 2.—A, Coronal section of the brain to show an astrocytoma (Grade I) of the left thalamus involving the internal capsule and lenticular nucleus (Case 6). B, Coronal section of the brain to show the vascular glioblastoma of the left optic thalamus invading the internal capsule (Case 7). C, Coronal section of the brain to show an astrocytoma (Grade I) of the left optic thalamus involving the internal capsule (Case 9). D, Coronal section of the brain to show an astrocytoma (Grade III) of the thalamus and basal ganglia invading the internal capsule. There is a recent hæmorrhage into the tumour (Case 12).

To illustrate article by Wylie McKissock and Kenneth W. E. Paine.

XUM

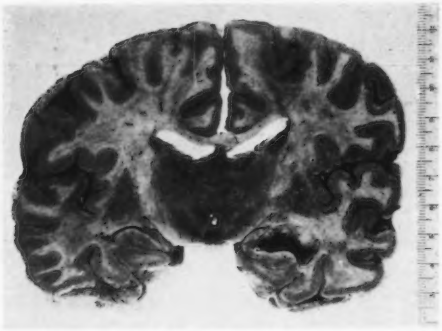


FIG. 3.—Coronal section of the brain to show the subependymal spread of the tumour from the thalami and the spread across the mid-line by the massa intermedia (Case 18).

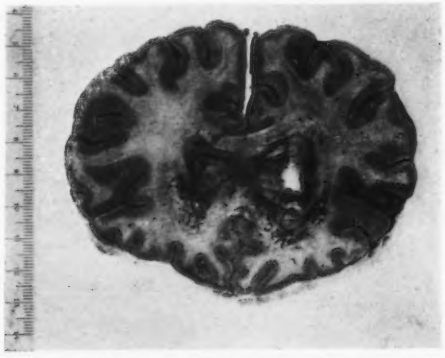


FIG. 4.—Coronal section of the brain to show the subependymal spread of a tumour occupying both thalami.

FIG. 5.—Brow-down postero-anterior ventriculogram to show the indentation into the third ventricle from the left side due to a nodule of a thalamic tumour. The marked hydrocephalus is also well shown (Case 10).

To illustrate article by Wylie McKissock and Kenneth W. E. Paine.

XUM

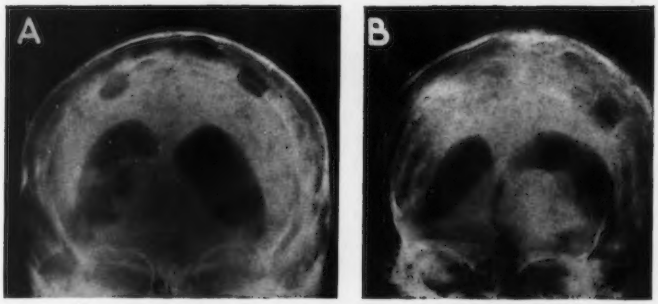


FIG. 6.—A, Postero-anterior brow-down ventriculogram to show the bowing of the third ventricle and the elevation of the body of the right lateral ventricle due to a tumour of the right optic thalamus (Case 1). B, Brow-down postero-anterior ventriculogram to show the bowing of the third ventricle to the right and the deformity of the medial aspect and floor of the left lateral ventricle due to a thalamic tumour (Case 11).

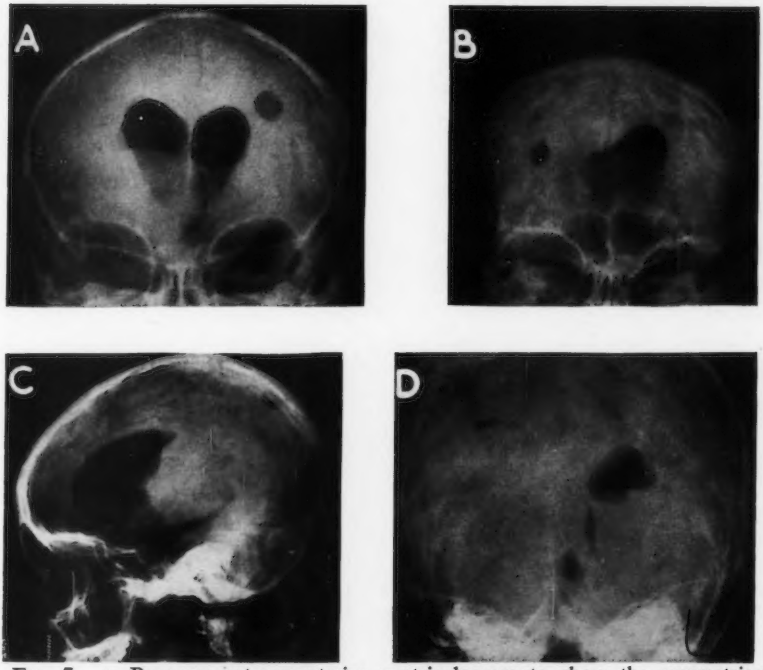


FIG. 7.—A, Brow-up antero-posterior ventriculogram to show the symmetrical dilatation of the lateral ventricles, the bowing of the third ventricle to the left and elevation of the body of the right lateral ventricle due to a tumour of the right thalamus (Case 1). B, Brow-up antero-posterior ventriculogram to show the dilatation of the left lateral ventricle and the third ventricle with bowing of the third ventricle to the right and elevation of the body of the lateral ventricle due to a left thalamic tumour (Case 6). C, Brow-up lateral ventriculogram to show the symmetrical hydrocephalus of the lateral ventricles, the dilated anterior portion of the third ventricle and the filling defect lying behind the foramen of Monro between the body and the temporal horn of the left lateral ventricle. The third ventricle is obstructed posteriorly (Case 7). D, Brow-down half-axial ventriculogram to show the displacement of the third ventricle and upward displacement of the trigone due to a large right thalamic tumour (Case 23).

To illustrate article by Wylie McKissock and Kenneth W. E. Paine.

XUM

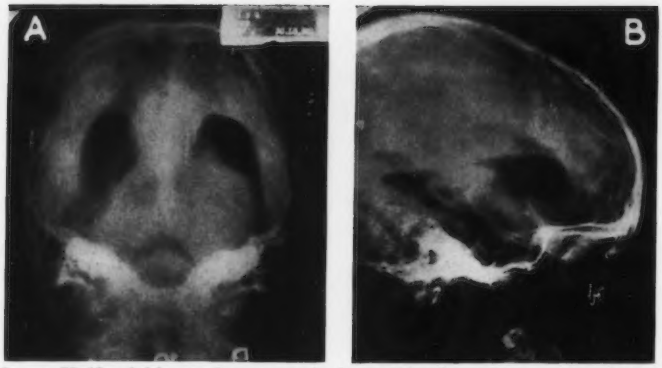


FIG. 8.—A, Half-axial brow-down ventriculogram to show the outward displacement of the right temporal horn and backward displacement of the trigone (Case 5). B, "Hanging Head" ventriculogram to show the downward displacement of the temporal horn by a calcified thalamic tumour (Case 5).

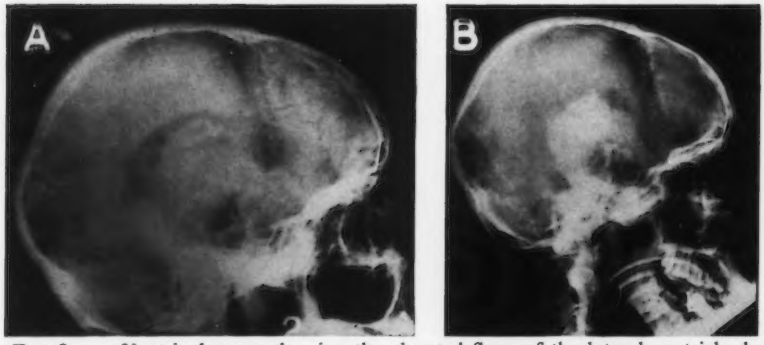


FIG. 9.—A, Ventriculogram showing the elevated floor of the lateral ventricle due to a mass in the thalamus. B, Vertebral angiogram showing an angioma in the thalamus of the same patient.

To illustrate article by Wylie McKissock and Kenneth W. E. Paine.

XUM

XUM

XUM

(6) Stress is laid upon the presence of a group of disturbances of ocular muscles, intrinsic or extrinsic as a characteristic disturbance to be found in patients with tumours of the thalamus.

Our thanks are due to Dr. P. M. Daniel of the Radcliffe Infirmary, Oxford, for the post-mortem findings in one case and the illustrations, figs. 3 and 4, of that case.

We are indebted to Mr. Prickett of the Medical Photographic Department, The National Hospital, Queen Square and Mr. Lytle, Medical Artist, at the Hospital for Sick Children, Great Ormond Street, for the tables and illustrations.

Dr. E. A. Carmichael was kind enough to give advice concerning the preparation of this paper.

REFERENCES

BRAMWELL, B. (1899) *Brain*, **22**, 1.
BRZEZICKI, E. (1929) *Schweiz. Arch. Neurol. Psychiat.*, **25**, 56.
CLARKE, J. M. (1898) *Brain*, **21**, 305.
DAVIDOFF, L. M., and EPSTEIN, B. S. (1950) The Abnormal Pneumoencephalogram. London, pp. 209-215.
DEJERINE, J., and ROUSSY, G. (1906) *Rev. neurol.*, **14**, 521.
ELVIDGE, A., PENFIELD, W., and CONE, W. (1937) *Res. Publ. Ass. nerv. ment. Dis.*, **16**, 107.
GOLLA, F. L. (1931) *Proc. R. Soc. Med.*, **24**, 1000.
HEAD, H., and HOLMES, G. (1911) *Brain*, **34**, 102.
HYNDMAN, O. R. (1938) *Arch. Surg., Chicago*, **36**, 245.
——, and VAN EPPS, C. (1939) *Arch. Surg., Chicago*, **39**, 792.
MCCONNELL, L. H., and CHILDE, A. E. (1937) *Arch. Neurol. Psychiat., Chicago*, **37**, 56.
METTLER, F. A., DAVIDOFF, L. M., and GRIMES, R. (1947) *Arch. Neurol. Psychiat., Chicago*, **57**, 423.
ODY, F. (1932) *Arch. Neurol. Psychiat., Chicago*, **27**, 249.
PENMAN, J., and SMITH, M. C. (1954) *Spec. Rep. Ser. med. Res. Coun., Lond.* No. 284.
PFEIFER, B. (1910) *Arch. Psychiat. Nervenkr.*, **47**, 558.
SCIARRA, D., and SPROFKIN, B. E. (1953) *Arch. Neurol. Psychiat., Chicago*, **69**, 450.
STANLEY, D. (1898) *Brain*, **21**, 339.
SMYTH, G. E., and STERN, K. (1938) *Brain*, **61**, 339.
TORKILDSEN, A. (1947) Ventriculocisternostomy. A Palliative Operation in Different Types of Non-communicating Hydrocephalus. Oslo.
—— (1948) *J. Neurosurg.*, **5**, 249.
WILSON, S. A. K. (1955) Neurology. Second Edition. London, Vol. **3**, p. 1822.

XUM

THE EFFECTS OF REPEATED STIMULI UPON EEG AND VASOMOTOR ACTIVITY DURING SLEEP IN MAN

BY

G. PAMPIGLIONE AND BRIAN ACKNER

(From The Maudsley Hospital and The Institute of Psychiatry, London University)

A STIMULUS applied to a sleeping subject may evoke a number of bodily responses. Some of these responses are easily recognizable and can be directly observed, e.g. a movement of the limbs, a change in amplitude or rate of respiration, opening of the eyes and awakening. Other responses are less apparent, being detected only by delicate measurements of some physiological variables. The electrical activity of the brain may show large variations in response to mild sensory stimuli during sleep (K. complexes). The vasoconstrictor response to sensory stimuli is a particularly sensitive one, present in both the waking and sleeping state. Variations in both these fields may or may not be accompanied by visible movements of the subject or by awakening.

We have been interested in the relationships between the electrical activity of the brain (EEG) and the pulse volume waves (finger plethysmography), and have previously found that some of the variations in amplitude of the pulse volume waves (vasoconstrictions) are often preceded by changes in the EEG with a fairly constant time-interval (Ackner and Pampiglione, 1955). Previous studies had shown that there was a similarity between some "spontaneous" changes in the EEG during sleep and the EEG responses (K. complexes) which may be evoked by a sensory stimulus (Loomis *et al.*, 1938; Brazier, 1949; Pampiglione, 1953). Our studies revealed some relationship between spontaneous and evoked EEG and plethysmographic changes, and it seems likely that both the K. complexes and the vasoconstrictions represent common bodily responses to various alerting stimuli (Ackner and Pampiglione, 1957).

Repetition of the same stimulus during sleep in man, results in less constant or recognizable K. complexes (Pampiglione, 1952, 1953) and similar features have been demonstrated for the "arousal" reaction in the EEG of cats (Sharpless and Jasper, 1956).

The present study was carried out to investigate the vasomotor and EEG responses in man to the same stimulus repeated at regular time-intervals, during sleep.

XUM

Material and Method

Simultaneous EEG and finger plethysmographic records were taken in 17 subjects (2 members of the staff and 15 patients suffering from various psychiatric disorders). 2 patients were retested once and another was retested twice, making a total of 21 experiments. An equal number of experiments had to be discarded because sleep was not obtained, or was not sufficiently prolonged. All the records were taken in the afternoon while the subject slept spontaneously (2 patients and 2 staff members) or during sleep induced by administration of oral quinalbarbital ($1\frac{1}{2}$ to $4\frac{1}{2}$ grains). The recording technique used has previously been described (Ackner, 1956).

The onset of sleep was determined by an arbitrary criterion and was taken as occurring one minute after the disappearance of alpha rhythms with appearance of slower activities and often "sleep spindles." With a little practice, the onset of sleep as defined above could be easily recognized. The 21 records described in this paper are those in which the subjects remained asleep either throughout, or for most of the experiment.

Twenty-five minutes after the onset of sleep a stimulus was applied and at regular 20 seconds intervals thereafter the stimulus was reapplied nineteen more times and then no further. A low-pitched (300 c/s) low-intensity note was found to be the most advantageous as good responses could be obtained, usually without waking the subject. The duration of the stimulus was half a second, the sound being kept constant in pitch and intensity for each experiment. 7 of the 17 subjects awakened during the series of stimuli (2 woke twice) but all fell asleep again, usually within one minute. In these subjects the stimulation was continued despite brief awakening.

Findings

A considerable variability was noticed in the EEG and vasomotor responses in each subject, and from one subject to another. While the subject was in a light sleep the first stimulus of the series usually evoked a K. complex followed with a delay of 3 to 4 seconds by vasoconstriction as indicated by a diminution of the amplitude of the pulse volume waves (fig. 1). On three occasions there was a short-lived return of alpha rhythms also followed by vasoconstriction. This combined EEG and vasomotor change was clearly seen in response to the first stimulus of the series in 18 out of 21 experiments, in 1 more such change was barely recognizable, and in 2 it was absent. In response to the second stimulus of the series, a similar number of recognizable EEG and vasomotor changes appeared (18 out of 21) always with the usual time-interval.

For the following stimuli, however, EEG and vasomotor responses appeared in several subjects to become independent, in the sense that one response could appear without the other. For example, a K. complex

XUM

might be evoked by the stimulus without being followed by vasoconstriction, or vice versa (fig. 2, stimulus 9). If vasoconstriction occurred it appeared with the usual delay of 3 to 4 seconds from the stimulus.

It was always difficult to assess whether, and how much the sleep level had changed after the first few stimuli and, as mentioned already, 7 of the subjects appeared to wake up for a short period but fell asleep again while stimulation continued. In some subjects, however, no EEG or vasomotor response was recognizable after a few stimuli (fig. 3, stimulus 3). We considered this lack of response to be an adaptation phenomenon. Such adaptation often occurred after the fourth or fifth stimulus (*see* Table I) but there was much variability between subjects.

TABLE I.—ANALYSIS OF EEG RESPONSES IN TWENTY-ONE EXPERIMENTS

Stimulus No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	X
Recognizable response	18	18	11	11	12	13	15	11	10	7	9	14	11	12	13	8	10	7	11	11	6
No response	2	2	6	8	7	4	2	4	4	6	4	5	7	5	3	9	8	6	7	3	11
Doubtful response	1	1	4	2	2	4	4	6	7	8	8	2	3	4	5	4	3	8	3	7	4
"Anticipation"	0	0	1	2	2	6	6	9	9	8	12	4	2	7	6	6	5	5	6	7	4

X=20 seconds after final stimulus.

(The EEG changes described as "anticipation," are considered separately from the EEG responses to the stimulus.)

For example, lack of response might occur after the fifth stimulus in one subject, but not until the fifteenth in another. Sometimes there was a tendency for some subjects to continue to respond with EEG more than with vasomotor changes or vice versa.

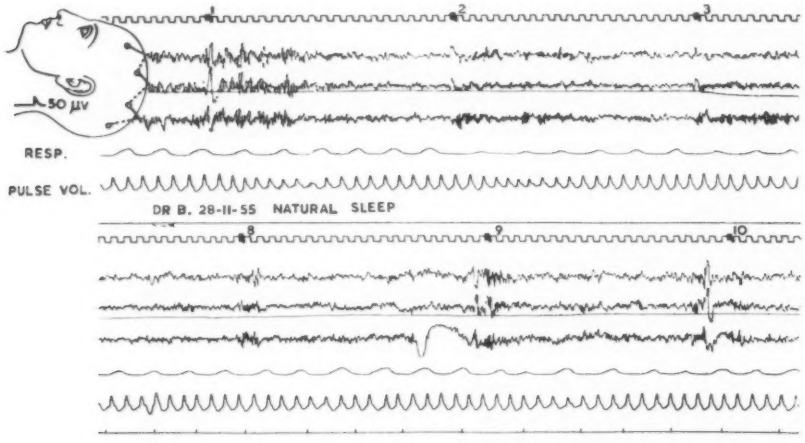


FIG. 1. (*To be continued, see next page*).

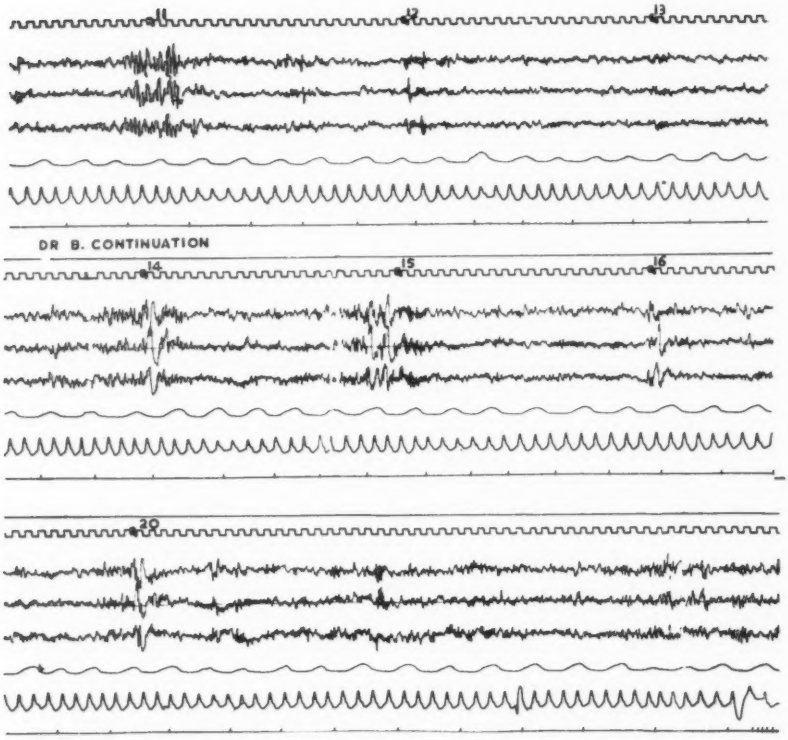


FIG. 1.—Spontaneous sleep in control subject. This record shows "anticipation" (stimulation 9–10–11–15–16); "adaptation" (stim. 13); "loss of adaptation" (stim. 14); and EEG changes 20 and 40 seconds after the last stimulus of the series.

Adaptation usually did not appear to last for more than two or three stimuli, especially for the EEG responses, and a K. complex often followed by vasoconstriction would reappear after a further stimulus. Sometimes this loss of adaptation would occur in both fields together as a marked response.

After several repetitions of the stimulus at 20 seconds intervals, a new EEG phenomenon began to occur. This appeared as a change indistinguishable from a K. complex, preceding the stimulus for not more than two seconds and sometimes followed by vasoconstriction (fig. 1, stim. 9, 10, 11, 15, 16; fig. 2, stimulus 8). We considered this to be a phenomenon of anticipation, as though the timed stimulus was expected. This anticipatory phenomenon could occur early in the series of stimuli (*see* Table I) but was more common preceding the eighth to the eleventh repetition. At one time or another anticipation occurred in nearly all subjects and was

XUM

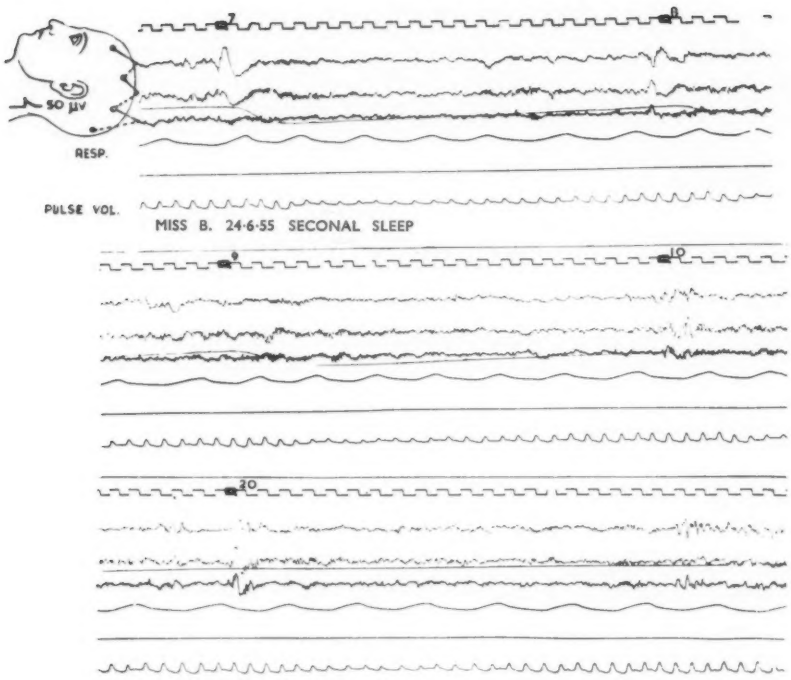


FIG. 2.—Quinalbarbital induced sleep in psychoneurotic patient. "Anticipation" at stimulus 8. "Adaptation" of EEG with preserved vasoconstriction after stim. 9. EEG change at the time of missing stimulus about 20 seconds after stimulus 20.

easily recognizable. Again, as was noticed for adaptation phenomena, anticipation did not persist for more than three or four stimuli, although it could reappear later, after either a period of ordinary responses or adaptation.

When anticipatory EEG changes were followed by vasoconstriction there was the usual 3 to 4 seconds delay, similar to that seen associated with ordinary K. complexes. As vasoconstriction would often follow a stimulus without a K. complex being recognizable, we investigated the possibility that vasoconstriction might occur alone as an "anticipatory response." No definite opinion can be expressed on this point for not only is the vasomotor response delayed, but its onset is not sufficiently rapid to be accurately timed.

Special consideration was given to the last stimulus of the series and to any phenomena which might occur 20 seconds later at about the time when a further stimulus might be expected though never given. No recognizable change occurred in 11 of the 21 experiments, but some EEG

XUM

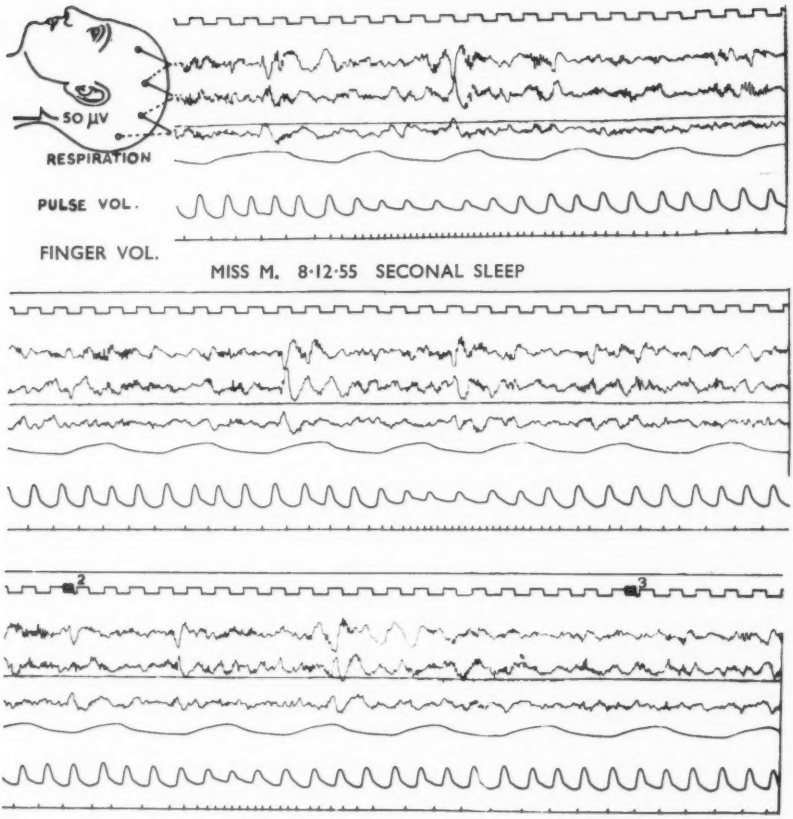


FIG. 3.—Quinalbarbital induced sleep in psychoneurotic patient. Spontaneous K. complexes followed by "secondary K. complexes" at fairly constant intervals. Only the first ones are followed by vasoconstriction (upper two tracings). After stim. 2 a K. complex is followed by "secondary K. complex" with delay similar to that of the spontaneous ones. EEG and vasomotor "adaptation" at stimulus 3.

change about the time of the "expected" but missing stimulus was seen on ten occasions. On four of these occasions the EEG changes appeared just before the time of the missing stimulus, as for an anticipatory response, but on six occasions these changes appeared soon after the time of the missing stimulus (fig. 2). One of the subjects (fig. 1) actually woke up forty-five seconds after the last stimulus of the series having shown EEG changes about 20 and 40 seconds after the twentieth stimulus. Vasoconstriction followed the EEG changes on four occasions but was never seen alone.

XUM

In a few subjects EEG and/or vasomotor changes occurred at times a number of seconds removed from the stimulus. As these changes did not bear a close time-relationship to the stimulus they were considered to be spontaneous in nature or perhaps related to the earlier K. complex which had followed the stimulus.

The experiment was repeated on four occasions with a few weeks interval, and the results confirmed the great variability not only from one subject to another, but even in the same subject. There was, however, a tendency for some subjects to respond more either in the vasomotor or in the EEG field. No substantial difference was noticed in the type and variability of responses between the normal subjects and the patients, and whether sleep was spontaneous or induced by barbiturates.

Discussion

The usual EEG response to an alerting stimulus during light sleep is an immediate K. complex followed by a digital vasoconstriction with an interval of 3 or 4 seconds. The present study reveals that when stimuli are repeated at 20 seconds intervals the EEG and vasoconstrictor responses appear fairly parallel for the first two or three stimuli of a series. Thereafter, however, one response may appear without the other and sometimes no response at all is recognizable. Phenomena considered as adaptation, loss of adaptation, anticipation and response at the time of a missing stimulus, tend to occur in a variable manner.

It is commonly recognized that the bodily responses elicited by a stimulus during the waking state, depend to a certain extent upon some qualities of the stimulus (intensity, modality, duration, etc.) and upon the subject's condition at the time. For example, knocking at the door of a subject reading his newspaper may not elicit the same bodily response that might be expected from his neighbour, who was expecting a telegram. It is also known that during sleep there seems to be some possibility of discriminating between stimuli. For example, a mother of many children may wake only when the infant cries; and most people continue to sleep despite the intermittent noise of cars or trains outside their bedroom windows. It has also been demonstrated that calling the sleeping subject by name might evoke greater EEG changes than would be obtained by a whistle or other noises (Li and Jasper, 1952) although the physical properties of these stimuli were not matched.

In our investigation, however, it appeared desirable that the repeated stimulus should, as much as possible, be devoid of "significance" for any subject. An auditory stimulus in the form described above was preferred to other forms of stimulation, as it could easily be repeated with suitable constant characteristics. The decision to apply a total of 20 stimuli was an arbitrary one.

The interval between stimuli was kept constant in order to introduce

deliberately a time factor in the experiment. It was difficult, however, to establish which interval might be the most profitable. Too long an interval would protract the total duration of the experiment and sleep might not be maintained. Too short an interval between stimuli might coincide with some spontaneous fluctuations of either vasomotor or cerebral activities. However, the constancy of a fairly short time-interval between repeated stimuli might be better appreciated than that of a long time-interval. After preliminary trials with various intervals, a constant 20 seconds interval between stimuli appeared the most satisfactory.

Our findings revealed considerable variability of EEG and vasomotor responses, particularly from the third stimulus onwards (*see* Table I). One of the most common phenomena observed was adaptation, namely, the lack of appearance of EEG and/or vasomotor responses following a stimulus. However, Roth, Shaw and Green (1956), in a study of K. complexes, were unable to find evidence of adaptation to repeated stimuli in their subjects. These authors suggested that the occasional lack of response to a stimulus in their subjects was probably due to chance occurrence. It is difficult to understand their approach to the problem as they give the term K. complex a meaning at variance with that of the original description by Loomis *et al.* (1938), and commonly accepted in electroencephalography. However, it appears from their table that the stimuli did not evoke K. complexes for the first fifteen stimuli while, later, EEG responses were evoked fairly regularly. This is probably related to the fact that their subject was receiving a slow intravenous injection of Thiopentone, for it is difficult to elicit K. complexes with mild stimuli during the early phase of barbiturate narcosis (Ackner and Pampiglione, 1955). In our present study the early phase of barbiturate narcosis was avoided by beginning stimulation twenty-five minutes after the onset of sleep. In addition it is not clear from Roth, Shaw and Green's paper whether the stimuli were given at regular intervals, as from their illustration it appears that such intervals, though regular at first, varied on occasions later. The nature of the stimulus they employed did not appear to be constant, and in fact in addition to auditory stimuli, pin-pricks were employed on occasions. The importance of the constancy of both the stimulus and the time-interval between stimuli in our investigation should be emphasized. In a recent paper (Sharpless and Jasper, 1956) the "arousal reaction" in the EEG of 35 cats was studied and it was found that repetition of the same stimulus at many minutes intervals may evoke increasingly less marked arousal reactions during spontaneous sleep.

Adaptation can be considered to represent the loss of the alerting value of the stimulus. In other words, as a result of the repetition of the same stimulus its novel significance is lost and alerting responses cease to occur. Repetition of the same stimulus during the waking state has long been

XUM

known to cause early and prolonged adaptation of both the EEG and peripheral responses. However, it appears that during sleep such adaptation is usually not maintained for long and responses to stimuli appear again until adaptation is once more established.

It is not easy to define the possible mechanisms that underlie the appearance of responses we have described as "anticipatory." All our subjects but three, showed at one time or another, one or more of these EEG changes occurring within two seconds before the time of the next stimulus. It has been suggested that the slow wave of the K. complex might be related to a sleep-protecting mechanism, rather than being a manifestation of arousal. In the light of this working hypothesis the anticipatory phenomena could be regarded as representing a conditioned defence against the expected stimulus. It is probable that the preliminary phases of conditioning to the time-interval between stimuli occurred in connexion with both adaptation and anticipation and that these phenomena are somehow related. Evidence of conditioning to the time-interval does not begin to appear until after the third stimulus and this is perhaps to be expected, for not until three stimuli have been given can the existence of the fixed interval between stimuli be recognized.

Very little has been found in the literature on the correlation of cerebral and autonomic phenomena with alterations of consciousness and arousal in man. Jung has contributed to this subject with a number of publications (Jung, 1939, 1941, 1954; and Weber and Jung, 1940). He studied the EEG, respiratory and autonomic responses (pulse-rate, finger plethysmogram and galvanic skin response) in epileptics and in normal subjects, and concluded that "a system regulating the arousal effects after sensory stimuli can be activated in normal as well as in pathological alterations of consciousness." The autonomic responses as recorded by Jung (1954) showed "only minor changes[1] in different states of consciousness, whereas the EEG had very different forms of arousal responses, varying with the level of consciousness." The autonomic responses to stimuli "did not change in different states of consciousness, except that conditioning and expectation of the stimulus tend to suppress and diminish the reactions in the waking state." As a corollary to such interpretation Jung (1954) suggests that "the appearance of autonomic responses during sleep to otherwise ineffective stimuli, indicates that sleep may eliminate a conditioned suppression of these responses, which has developed in the waking state." Apparently no adaptation phenomena ("habituation" of other workers) were noticed by Jung during sleep either in the EEG or vasomotor responses. However, there is no evidence that in his experiments the various stimuli used during sleep were repeated at regular intervals.

The occurrence of conditioning phenomena in the EEG during sleep, has, however, been accepted by other workers (Li, Jasper and Henderson,

[1] ? differences.

1952; Pampiglione, 1953; Larsson, 1956). In previous EEG studies it was suggested that a trace or "memory" of some quality of a stimulus may persist during sleep and that the time-interval between stimuli might be relevant in the establishment of adaptation phenomena in the EEG (Pampiglione, 1952; Pampiglione and Martin, 1954; Chafetz and Cadilhac, 1954). From our observations it may be postulated that the trace or memory of the time-interval between stimuli is stored and "recognized" somewhere in the brain of the sleeping subject, and that phenomena perhaps equivalent to expectation occur during sleep. There is little chance of direct proof of this hypothesis, though the presence of EEG and occasional vasomotor changes at about 20 seconds after the last stimulus of the series, would tend to give it some support.

It is a matter for speculation whether the absence of a stimulus, at the time it might have been expected, should be considered as a new stimulus in itself. This problem cannot be solved on the basis of our limited number of experiments, but it may be important in relation to theories of learning and conditioning. In fact, in our investigations the EEG changes occurring 18 or 19 seconds after the last stimulus in four subjects can be considered as anticipatory phenomena. However, the EEG changes that occurred in six subjects, just over 20 seconds after the last stimulus, could be considered according to preferred theory as either a response to the "memory" of the time-interval (conditioning); or a response to a new stimulus created by the absence of an expected stimulus; or as a chance occurrence.

It appears from our studies that there is a considerable variability in the manner in which a subject responds to alerting stimuli during sleep. Adaptation may be manifested early in some, late in others and in many it cannot be maintained for long. Anticipatory responses may be common in some but rare in others but some phenomena of conditioning appear in all subjects. Perhaps this variability is related to differences in the psychophysiology of the individual, but at the moment our material is too limited in number and variety of subjects for this to be examined. However, individual differences in physiology of alerting may be of significance in the study of those disorders commonly considered to be related to emotional stress and further study along these lines may well be rewarding in this respect.

Summary

Simultaneous EEG and finger plethysmography have been studied on normal subjects and psychiatric patients during natural and barbiturate-induced sleep. An auditory stimulus of fixed characteristics was repeated twenty times at 20 seconds intervals. The responses evoked were similar in most subjects for the first few repetitions, but later showed a considerable variability.

XUM

Phenomena considered as adaptation, loss of adaptation, anticipation and response at the time of a missing stimulus are described. These cerebral and vascular changes are considered to be related to conditioning and probably determined by the use of a fixed time-interval between stimuli.

ACKNOWLEDGMENTS

Part of this work was supported by a grant from the Research Committee of the Board of Governors of Bethlem Royal and The Maudsley Hospitals to whom the Authors are indebted. We should also like to thank Dr. Denis Hill for his encouragement.

REFERENCES

ACKNER, B. (1956) *J. Psychosom. Res.*, **1**, 21.
——, and PAMPIGLIONE, G. (1955) *Electroenceph. clin. Neurophysiol.*, **7**, 153.
——, —— (1957) *J. Neurol. Neurosurg. and Psychiat.*, **20**, 58.
BRAZIER, M. A. B. (1949) *Electroenceph. clin. Neurophysiol.*, **1**, 195.
CHAFETZ, M. E., and CADILHAC, J. (1954) *Electroenceph. clin. Neurophysiol.*, **6**, 565.
JUNG, R. (1939) *Nervenarzt*, **12**, 169.
—— (1941) *Nervenarzt*, **14**, 57.
—— (1954) In "Brain Mechanism and Consciousness," p. 310. Blackwell, Oxford.
LARSSON, L. E. (1956) *Electroenceph. clin. Neurophysiol.*, **8**, 631.
LI, C. L., JASPER, H., and HENDERSON, L. (1952) *Electroenceph. clin. Neurophysiol.*, **4**, 513.
LOOMIS, A. L., HARVEY, E. H., and HOBART, G. A. (1938) *J. Neurophysiol.*, **1**, 413.
PAMPIGLIONE, G. (1952) *Rev. neurol.* (*Paris*), **87**, 197.
—— (1953) Vth International Neurological Congress, Lisbon, **1953**, Vol. 2, p. 175, Lisbon.
——, and MARTIN, F. (1954) *Schweiz. Arch. Neurol. Psychiat.*, **71**, 277.
ROTH, M., SHAW, J., and GREEN, J. (1956) *Electroenceph. clin. Neurophysiol.*, **8**, 385.
SHARPLESS, S., and JASPER, H. (1956) *Brain*, **79**, 655.
WEBER, W. C., and JUNG, R. (1940) *Z. ges. Neurol. Psychiat.*, **170**, 211.

XUM

NEUROLOGICAL COMPLICATIONS OF THE RETICULOSES

BY

E. C. HUTCHINSON, B. J. LEONARD, C. MAUDSLEY AND P. O. YATES

(*From the University of Manchester and the Manchester Royal Infirmary*)

INVOLVEMENT of the nervous system is a well-recognized complication of certain of the reticuloses and many case reports and reviews on this subject have been published, the most complete in recent years being that of Sparling, Adams and Parker (1947). However, much of the literature on the subject of neurological involvement in the reticuloses is based on a retrospective study of pathological material and such an approach, of necessity, tends to neglect the early diagnostic difficulties which confront the physician. This further study that we have carried out, has not only brought into prominence these early difficulties in diagnosis but has also drawn our attention to certain unusual clinical and pathological features. These latter are, we believe, of some importance since they are not necessarily dependent on direct invasion of the nervous system by reticular tissue. For these reasons we are presenting the results of this further study.

CLINICAL MATERIAL

The clinical material on which these observations are based consist of 229 patients who have attended the Manchester Royal Infirmary during the past twenty years. The diagnosis of reticulosis has been based either on biopsy or necropsy material and only where the diagnosis was established by these means was the patient included in this study. Leukæmia, myelomata and lipoid storage disease have not been included in this study.

RESULTS

Since the primary object of the investigation has been to study the various types of neurological abnormality as they are seen by the physician, and since there is no pattern of neurological involvement constant for any of the various types of the reticulosis, we are presenting our results under clinical rather than pathological headings. It will be apparent from the numbers in each group that patients are referred to more than once in discussing the various types of neurological abnormality. This involvement of the nervous system at different levels (and

XUM

sometimes by different pathological processes) is sufficiently frequent to be one of the characteristics of the neurological lesions encountered.

The case histories presented have been chosen to draw attention to the less commonly recognized types of neurological lesion seen in the reticuloses. Patients with neurological signs directly resulting from invasion by reticular tissue have not been described in full since there are many detailed descriptions of this sequence of events in the literature.

Abnormalities in the nervous system were observed in 45 of 229 patients. The frequency in the various types of the reticuloses is shown (Table I).

TABLE I.—THE INCIDENCE OF NEUROLOGICAL INVOLVEMENT IN THE VARIOUS TYPES OF RETICULOSIS

Histological type of reticulosis	*No. of cases*	*No. with C.N.S. involvement*
Hodgkin's granuloma	160	32
Hodgkin's paragranuloma	8	0
Lymphosarcoma	14	3
Lymphoid follicular reticulosis (Brill-Symmers)	14	1
Reticulosarcoma	33	9
Total	229	45

The details of the neurological abnormalities in each type is shown in Table II. The abnormalities will be discussed under the following headings:

(1) Mental changes.
(2) Epilepsy.
(3) Changes in the optic fundus.
(4) Intracranial lesions of sudden onset—with focal signs.
(5) Lesions of the spinal cord.
(6) Peripheral nerve lesions.

MENTAL CHANGES

In the past little emphasis has been placed on changes in personality in the course of Hodgkin's disease. The majority of authors have regarded such changes as rare (Winkelman and Moore, 1941; Jackson and Parker, 1945).

In 17 patients in this series mental changes were noted and sometimes dominated the clinical picture. In 2, mental changes followed an episode of convulsions and in both it appeared probable that an intracerebral vascular accident was responsible both for the convulsions and for the subsequent personality change. In the remaining 15 patients the mental change was not related to any sudden episode and in 6 of these, who later came to post mortem, there was no evidence of intracranial deposits of reticular tissue.

The mental change in this group varied from a moderate degree of

depression—sufficiently severe for one case to receive psychiatric treatment for six months before the underlying reticulosis declared itself—to a rapidly developing dementia occurring in the terminal stages of disease and sometimes being the first sign of the general deterioration which was shortly to follow. The following case histories illustrate these two types.

Case Report. Male aged 42 (*Case* 2)

The patient was admitted to hospital for investigation in 1951 with a history of depression and lassitude of twelve months' duration. The first symptom was depression which appeared gradually and lasted for periods varying from two to three weeks. A mild personality change, consisting mainly of unaccustomed irritability with his near relatives, was also noted. Two months later he complained of tingling in the upper limbs and trunk which came on in short episodes lasting a few seconds only; the tingling began in the mid-sternal region and radiated to the chin and arms and there was no associated impairment of consciousness or of motor power in the limbs. The only other significant feature was loss of 2 st. in weight. The positive finding on examination was a discrete enlargement of the supraclavicular lymph nodes. The only abnormality in the nervous system was a loss of the tendon reflexes in the upper and lower limbs, without impairment of power or disturbances of sensation. The blood count, sternal marrow and the radiological examination of the chest were normal.

The cerebrospinal fluid was clear and colourless with a resting pressure of 140 mm. of water; 1 lymphocyte per c.mm.; protein 60 mg./100 ml.; globulin (Pandy) slight opalescence; Lange gold curve 0000000000.

A biopsy of one of the cervical nodes showed Hodgkin's disease.

Treatment with intravenous nitrogen mustard produced some improvement in his general condition, and this was maintained for the next eighteen months. Further weight loss was then noted and diarrhœa developed. (Both persisted until the time of his death eighteen months later.) He then complained of constant severe backache, later shown by radiological examination to be due to neoplastic infiltrations of the pelvis, the femur and the lumbar spine.

Two months before death an abnormality in the optic fundi was noted for the first time. The disc margins became obscured and gradually the whole disc assumed an appearance which resembled papillœdema (fig. 1). The abnormal appearance of the fundi persisted together with the areflexia until the time of his death two months later from a severe melæna. The cerebrospinal fluid showed, two days before death, a resting pressure of 160 mm. of water: cells 4 lymphocytes per c.mm.; protein 110 mg./100 ml.: globulin (Pandy) slight opalescence: Lange gold curve 0011000000. Blood examination Hb. 9·3 mg. per 100 ml.; R.B.C. 3,300,000 per c.mm.; W.B.C. 4,800 per c.mm.; polymorphs 72 per cent; lymphocytes 17·0 per cent; monocytes 10·0 per cent; basophils 0·5 per cent; eosinophils 0·5 per cent.

Necropsy.—The body was that of a wasted man showing no œdema, jaundice, or other abnormal pigmentation. The skin and mucous membranes were pale. Apart from some pallor of the myocardium, the heart (325 grammes) was normal. The aorta and major arteries showed a moderate degree of atheroma. There was bilateral pulmonary œdema. Numerous petechial hæmorrhages were found in the peritoneum and mucosa of the alimentary tract. The liver weighed 1,540 grammes and showed a minor degree of portal cirrhosis. The spleen was enlarged (750 grammes) and contained numerous white nodules. The kidneys, pancreas, and adrenals were normal. The lymph nodes were enlarged in the aortic, axillary and inguinal groups. There were no meningeal deposits in the skull or spinal canal.

XUM

The brain and cord were macroscopically normal. The optic chiasma and both optic nerves showed swelling and fragmentation of some axons with "torpedo" swellings and end-bulbs (fig. 2). These changes were most marked in the median bundles of both nerves. Sections from many parts of the brain and spinal cord revealed no significant abnormality.

The peripheral nerves showed extensive demyelination with loss of axons and some neurilemmal proliferation (fig. 3). This was particularly marked in fine nerve twigs but it was also present in the large trunks where not all the bundles were affected to the same degree. There was little evidence of recent exacerbation of the condition. Nowhere was there any evidence of vascular disease or neoplastic compression such as could have produced peripheral nerve damage.

In the remaining 12 patients in this group the onset of mental symptoms coincided with a deterioration in the patient's condition, and was usually a sign that the disease was entering its final stages. The dementia was usually profound, the major signs being confusion and disorientation, but there were no localizing signs in the nervous system in the early stages of the dementia. Later when the patient sank into terminal coma (and this in our experience usually occurred within ten weeks of the appearances of the mental change) dilatation of the pupils and extensor plantar responses might be found. The following history is typical of this group.

Case Report. Male aged 28 (*Case* 3)

The patient first attended hospital in February 1954, complaining of enlarged cervical glands of five months' duration. A biopsy of one of the nodes confirmed the clinical diagnosis of Hodgkin's disease. The nervous system at that time was normal. A course of nitrogen mustard was given (a total of 18 mg. intravenously) and produced temporary reduction in the size of the glands. He improved and remained well for twelve months when the lymph nodes again increased in size; he lost weight and complained of severe sweating. A course of triethylene thiophosphoramide (total 175 mg.) was given over a period of six weeks which reduced the lymph nodes with distinct clinical improvement. The improvement was maintained for four months.

At the end of this period he began to lose weight rapidly, and the cervical nodes once more increased in size. A month after the onset of these symptoms mental change was noted for the first time—quite suddenly he became confused and disorientated, appearing dull and apathetic and, over the next fourteen days, he became profoundly demented.

He was admitted to hospital in a state of marked emaciation. Although drowsy he could be roused, and recognized his medical attendants. His speech was slurred. The disc margins in both fundi were blurred and there were many small hæmorrhages in both retinæ. There was a marked general weakness without any reflex or sensory change in the limbs. All the superficial lymph nodes were enlarged and scattered petechiæ were noted over the abdomen, chest, and limbs. Blood examination: Hb. 4·3 grammes per 100 ml.; R.B.C. 1,090,000 per c.mm.; W.B.C. 1,200 per c.mm.; polymorphs 45·5 per cent; lymphocytes 35·5 per cent; monocytes 10·5 per cent; eosinophils 2·5 per cent; basophils 0·5 per cent; myelocytes 5·5 per cent; platelets 30,000 per c.mm.

The patient died twenty-four hours after admission. For fourteen hours before death he was in deep coma, lying with both arms and legs rigidly extended with his pupils widely dilated and fixed to light. The plantar responses were now extensor.

XUM

The blood pyruvate estimated in a specimen taken just before the onset of the terminal coma was 4·9 mg. per 100 ml.

Necropsy.—The body was that of an emaciated man. There was no œdema or abnormal pigmentation of the skin, which showed several small petechiæ on the trunk. The heart was of normal size. The lungs were congested and very œdematous. The aorta and larger blood vessels showed very little evidence of atheroma. The alimentary tract was normal. The liver, which weighed 1,940 grammes, showed a diffuse pallor on section and some loss of lobular outline. The spleen weighed 400 grammes and contained nodules of white tissue. The right kidney weighed 220 grammes and was normal, the left weighed 80 grammes, and had fewer calyces than normal. (This small kidney showed no macroscopic or microscopic evidence of disease and it was concluded that the appearances were due to a congenital hypoplasia.) The cervical, axillary, mediastinal, and para-aortic lymph nodes were all enlarged. The microscopical appearances in these glands were typical of Hodgkin's granuloma.

Nervous system: Macroscopically the only significant lesions in the central nervous system were a few scattered foci of petechial hæmorrhage in the reticular tissue of the pons, in the wall of the third ventricle and in the subcortical white matter of the right parietal lobe. For the most part they were small in extent and in only two of the areas was any abnormality other than hæmorrhage discovered. In these areas there was a proliferative activity of the capillary endothelium with frequent mitotic figures (fig. 4). There was evidence of local tissue necrosis with fragmentation of the myelin sheaths and microglial phagocytic activity. There was also some astrocytic proliferation but there was no other inflammatory cell reaction. Though resembling in some ways the focal lesions of Wernicke's encephalopathy the distribution was atypical (Campbell and Biggart, 1939). The corpora mamillaria for example, were normal. Apart from these changes no other histological abnormality of the brain or spinal cord could be found. These petechial hæmorrhages in the brain were not thought to be due to thrombocytopenia, since abnormalities of the capillary walls were present, similar to those seen in Wernicke's encephalopathy. In this patient, as in Wernicke's disease, the pathological counterpart of a severe dementia was only a few scattered foci of capillary abnormality.

These 17 patients were grouped together on the basis of mental changes developing in association with the underlying reticulosis. The pathological material available for detailed study is limited in this group but nevertheless it seems probable on clinical grounds that mental change, developing either as an initial sign or as a later manifestation of the disease, may be due to more than one pathological lesion. In 2 patients (Case 1 and Case 2) the mental changes followed immediately an intracranial lesion of sudden onset. In one there were clinical signs of a focal lesion and in the other there was radiological evidence of cerebral atrophy. In both it was thought that the mental changes could reasonably be attributed to a single episode which may have had a vascular basis.

In the remaining 15 the picture was very different, the main difference being the mode of development. These 15 patients were not, however, entirely similar. The differences lie in the time of onset in relationship to the natural history of the disease and in the degree of mental change. Of these 15 patients 6 have been examined at necropsy, and although

XUM

dementia was present there was no obvious anatomical change within the brain. Finally in those patients with a severe terminal dementia where the blood pyruvate was examined it was found to be elevated, sometimes to very high levels.

(2) Epilepsy

Although no information on the frequency of convulsions as a complication of the reticuloses has been found in the literature, they are a well-recognized, although a rare, occurrence (Jackson, and Parker, 1945; and Sparling, Adams and Parker, 1947).

5 patients in this series had one or more convulsions. In 2, a series of attacks occurred over a period of forty-eight hours and thereafter no further attacks were noted. In the other 3 patients, the convulsions continued intermittently up to the time of death in 2 and are still persisting in the third. Two important and helpful clinical points were that in no case was epilepsy the sole manifestation of neurological involvement, and that in 4 of the 5 patients the diagnosis of a reticulosis had been established before the onset of epilepsy. The other neurological manifestations were spinal cord lesions in 2, dementia in 1, hemiparesis in 1, and peripheral neuropathy and papillœdema in the fifth patient. The time-interval between the diagnosis of the reticulosis and the development of epilepsy varied from one to six years.

If the onset of convulsions should precede the signs of a reticulosis, and other signs of neural involvement have not appeared, the diagnostic problem may be that of epilepsy of late onset with all its attendant difficulties. The patient to be described is an excellent example of these.

Case Report. Male, aged 62 (*Case* 4)

The patient was admitted to the Department of Neurology for investigation of personality change and an epileptic attack. The history commenced twelve months previously, the first symptom being an alteration in his personality. Both the patient and his relatives noticed that he had become irritable and forgetful and found it difficult to accomplish everyday tasks. These symptoms were progressive. Two days before admission to hospital, when preparing for bed, he suddenly fell to the ground unconscious, and had a major convulsion. He rapidly regained consciousness and on admission to hospital two days later, apart from some mild dementia, there were no abnormal signs in the nervous system. Investigations were as follows: the cerebrospinal fluid: resting pressure 150 mm. of water; clear colourless fluid; cells 1 lymphocyte per c.mm.; protein 80 mg. per 100 ml.; globulin (Pandy) opalescence; Lange gold curve 0001100000. A left carotid angiogram was carried out and the report was as follows: "The vascular pattern was normal. No radiological evidence of a space-occuping lesion."

It was felt that the finding of an elevation of the protein in the cerebrospinal fluid suggested that the underlying lesion might be neoplastic rather than degenerative but there was insufficient evidence to justify surgical exploration. He was therefore discharged to be kept under frequent out-patient review. Over the next six months his condition gradually deteriorated. Not only did the mental symptoms progress, but he also complained of a constant numbness in the feet. He was therefore

XUM

readmitted to hospital. Examination now showed that in addition to the dementia there was œdema of the optic discs. In the limbs there was a general loss of muscle bulk together with areflexia. Sensory testing showed impairment of pain appreciation to a level just below the knees and a well-marked increase of calf tenderness. The abdomen, normal on the previous admission, was now distended due to a combination of ascites and enlargement of the liver and spleen. The cerebrospinal fluid was again examined: Resting pressure 130 mm. of water; cells 1 lymphocyte per c.mm.; protein 75 mg. per 100 ml.; Lange gold curve 0000000000. The blood and marrow examination and liver function tests were normal. The fasting blood pyruvate was elevated (1·6 mg. per 100 ml.).

A biopsy of an enlarged cervical lymph node showed the histological appearances of Hodgkin's disease. He was given a course of intravenous nitrogen mustard (total dose 18 mg.) with little clinical improvement. The abdominal distension slowly increased; the signs and symptoms of peripheral neuropathy continued; he died suddenly at home two years after the onset of the illness. (A post-mortem examination was not made.)

(3) Abnormalities of the Optic Fundus

Abnormalities in the optic fundus are rarely mentioned in the literature although papillœdema has been described in both Hodgkin's granuloma and sarcoma with intracranial deposits and in reticulosarcoma of the cerebellum (Sparling, Adams and Parker, 1947).

17 patients in this series showed abnormalities in the optic fundus. In 2 patients optic atrophy and blindness developed as a result of direct invasion of the optic nerve from adjacent reticular deposits in the orbital bones in one case, and from the maxillary sinus in the other (figs. 5 and 6). In 9 other patients visual disturbances were due to retinal hæmorrhage. In each case the hæmorrhages were due to thrombocytopenia; such a development in the course of a reticulosis is in itself a bad prognostic sign and so it proved to be in these patients—7 of the 9 patients dying within six months.

7 of the patients, including 1 patient who also showed retinal hæmorrhage, developed papillœdema but there was no evidence of raised intracranial pressure. In 2 of the patients (Cases 2 and 4) the diagnosis of intracranial Hodgkin's deposits had been made on the basis of the fundal appearances. In 1 (Case 2) post-mortem examination did not reveal any intracranial deposits and in the other detailed clinical investigation failed to demonstrate increased intracranial pressure.

In the early stages of the fundal change, blurring of the nasal margin is observed, to be followed later by œdema of the nerve head and adjacent retina (fig. 1). Even when the fundal changes were well marked, there was only minimal impairment of visual acuity amounting to an inability to read small print. Detailed examination of the visual field in 3 patients revealed only a moderate constriction of the visual field to a 5 mm. white object on the Bjerrum screen. The blood pressure, renal function and blood counts were not constantly altered.

The blood pyruvate was examined in 5 patients and found to be

XUM

always raised. 3 of these 5 were given vitamins of the B group. One of them died ten days later; in the 2 still alive the vision returned to normal and the disc appearances returned to normal. The possible significance of these findings will be referred to later.

(4) Intracranial Lesions of Sudden Onset—with Focal Signs

Under this heading we have included 13 patients who, in the terminal stages of the disease suddenly developed signs of a lesion of cerebral hemisphere, brain-stem, or cerebellum. In 6 patients post-mortem examination confirmed the clinical diagnosis of intracranial hæmorrhage, and in 4 others the clinical picture and accessory findings gave good ground for believing that a cerebral hæmorrhage had occurred. In all patients there was evidence of aplasia of the bone-marrow, and the resulting thrombocytopenia was, no doubt, the basic cause of the intracranial hæmorrhage.

The following patient is typical of this group, and moreover is an example of more than one pathological process affecting the nervous system in the course of the reticulosis.

Case Report. Female, aged 50 (*Case* 5)

The patient was admitted to hospital for investigation of a persistent and non-productive cough. Radiological studies on her first attendance showed the mediastinal nodes to be enlarged, and biopsy of one of these nodes confirmed the diagnosis of Hodgkin's disease. A few weeks later she complained of an itching sensation over the trunk but more particularly over the hands, the soles of the feet and the toes. She complained of a continuous burning sensation in the feet, worse at night and the touch of bedclothes on the feet was unbearable. She also complained of shooting pains radiating from the mid-dorsal region. When examined twelve months after the onset of the illness there was marked pallor of the mucous membranes and a generalized dark-brown pigmentation of the skin accentuated over the face and neck, and the dorsum of the hands and forearms. The skin over the dorsum of the feet was dry, thickened and scaly. The supraclavicular lymph nodes were enlarged and the liver and spleen were palpable. There was no alteration of tone or power in the limbs, the reflexes were all brisk and the abdominal reflexes were absent. The left plantar response was clearly flexor but the right plantar gave a variable extensor response. There was hyperæsthesia to pin-prick over the soles of the feet, together with an increase of calf tenderness. There was a constant level to both pin-prick and light touch at the seventh thoracic segment. The spinal movements were full and the vertebræ were not tender to percussion. Radiographs of the chest confirmed the presence of a pleural effusion and the vertebræ were normal. Blood examination: Hb. 10·1 grammes per 100 ml.; R.B.C. 3,510,000 per c.mm.; W.B.C. 5,000 per c.mm.; polymorphs 71 per cent, lymphocytes 25 per cent, monocytes 4 per cent; platelets 20,000 per c.mm. The result of the pyruvate tolerance test was: fasting level 1·00 mg. per 100 ml. One hour after 50 grammes of glucose 1·1 mg. per 100 ml. Two hours after 50 grammes of glucose 0·9 mg. per 100 ml.

Treatment with nitrogen mustard only produced a transient relief of symptoms and she continued to complain of the dysæsthesiæ in the feet and of severe dyspnœa. She was admitted again to hospital where one night she complained of a sudden occipital headache and died in fifteen minutes. The duration of the whole illness was fourteen months.

XUM

Necropsy.—The body was that of a poorly nourished middle-aged woman. There was no jaundice or œdema. The skin was pigmented brown, especially on the arms and face, where it is normally exposed to light; it was roughened over the dorsum of the feet. The anterior mediastinum was occupied by a firm fibrous mass which replaced the thymus and was adherent to the posterior surface of the sternum. The mass involved also the upper lobe of the right lung which weighed 1,000 grammes. The left lung and the heart were normal. The alimentary tract, liver and spleen were normal. Both kidneys contained deposits of tumour about 1 cm. diameter in the medullary regions. Apart from the thoracic mass there was no other involvement of lymph nodes. Bone-marrow from the middle of the shaft of a femur was pale and fatty.

The skull and vertebral column and the meninges were free of tumour deposits. There was a recent large hæmorrhage into the foliæ of the right cerebellar hemisphere and blood had spread into the subarachnoid space around the basal structures. Apart from this terminal lesion no abnormality was found in the brain. The spinal cord was nowhere compressed and appeared quite normal.

Histologically the mediastinal tissue was typical Hodgkin's granuloma. In the brain there were a few small petechial hæmorrhages in the subcortical white matter, but otherwise no abnormality was noted. In particular no deposits of Hodgkin's tissue were found in any part of the central nervous system. The left eye and optic nerve were normal. The spinal cord showed few lesions, none of which were recent. There were a few small foci of loss of myelin sheaths and scarring in the dorsal columns of the cervical cord and in the neighbourhood of these foci there were perivascular aggregations of Marchi-positive granules, presumably in macrophages. Elsewhere in the thoracic cord these perivascular Marchi bodies were seen in the lateral columns, suggesting old myelin destruction but no obvious demyelination could be seen in myelin stained sections. Dorsal root ganglia were normal. Peripheral nerves (left median, right sciatic, right lateral and medial popliteal, and right sural were examined) showed a patchy loss of axons and myelin sheaths (fig. 7). There was some proliferation of neurilemmal cells in the regions of fibre loss. Nowhere was there any evidence of active myelin destruction.

(5) Lesions of the Spinal Cord

Cord lesions developing in the course of the reticuloses are undoubtedly the commonest neurological abnormality reported; Parkes Weber (1923), East and Lightwood (1927), Forrest (1927) all drew attention to destruction and dislocation of vertebral bodies with subsequent cord compression. In addition both Forrest (1927) and Allen and Mercer (1936) noted that intrinsic cord lesions could occur in Hodgkin's disease without compression of the cord by Hodgkin's tissue.

A lesion of the spinal cord developed in 21 of the patients in the present series. In 16 of these there was evidence of compression of the cord by granulomatous tissue spreading either from a vertebral body or the dura. The history of these patients was not remarkable except perhaps the rapidity with which the paraplegia may develop. Root pain was a constant complaint in all of these 16 patients. In 4 the development of cord compression was the first intimation of the disease and in these, as in the remainder of the group, the development of a cord lesion indicated a bad prognosis. The longest survival after signs of a cord lesion appeared was twenty months.

XUM

In 5 patients there was no evidence of compression of the cord to account for the cord signs. 3 patients came to post-mortem and in 2 others the accessory investigations, including myelography, showed no sign of local cord compression. The recognition of this group has more than theoretical importance since it is difficult, if not impossible, to assess them on clinical grounds alone. If it is proposed to use radiotherapy in the treatment of a cord lesion then it is essential that myelography should be used to determine the presence or absence of compression. The following case report illustrates the clinical difficulties that may occur.

Case Report. Male, aged 42 (*Case* 8)

This history began in 1951, the first complaint being of "lumps in the neck." On examination both the cervical and the axillary glands were enlarged and the spleen was palpable 4 cm. below the costal margin. Biopsy of a cervical node confirmed Hodgkin's disease. He was given three injections of nitrogen mustard (total 18 mg.) and the glands diminished in size. He remained well until September 1954 when further weight loss occurred. In addition to the change in his general condition he now complained of heaviness and weakness of the legs. At that time there was a sensory level at the sixth thoracic dermatome and the right plantar response was extensor. The cervical and axillary glands had once more enlarged and the liver and spleen were again palpable. Radiographs of the spine were normal.

His general condition improved after a further four injections of nitrogen mustard (total 24 mg.), and pain in the back, a symptom becoming prominent before treatment, was relieved. The neurological signs remained unchanged although the function of the limbs improved. The improvement was maintained for ten months when weakness of the legs rapidly returned, he lost weight and complained of anorexia. The weakness of the legs progressed rapidly to a complete paraplegia with retention of urine. Again the radiographs of the vertebræ were normal and the cerebrospinal fluid showed a clear colourless fluid with normal dynamics; cells 8 lymphocytes per c.mm.; protein 80 mg. per 100 ml.; globulin (Pandy) slight excess; Lange curve 0011110000. Pyruvate tolerance test—fasting level 1·2 mg. per 100 ml.; half an hour after 50 grammes of glucose—1·6 mg. per 100 ml.; one hour after glucose—1·6 mg. per 100 ml.; one and a half hours after glucose 1·3 mg. per 100 ml.

It was felt that the paraplegia was due to compression by extradural deposits of Hodgkin's tissue and a further course of nitrogen mustard was given. Subsequently there was little change in his general condition although he was able to walk with the aid of sticks. Following a course of vitamin B by mouth (Becosyn Forte (Roche) 6 tablets per day for fourteen days) the blood pyruvate fell to normal limits, (fasting level 0·8 mg. per 100 ml.). After taking 50 grammes of glucose 0·8 mg., 0·9 mg., 0·6 mg. per 100 ml. of blood were the levels at a half, one and one and a half hours respectively. Blood examination: Hb. 2·7 grammes per 100 ml.; R.B.C. 1,100,000 per c.mm.; W.B.C. 1,500 per c.mm.; platelets 10,000 per c.mm.

General weakness, lassitude, and increasing heaviness of the legs were prominent symptoms over the next few weeks in spite of continuing the same vitamin therapy. Loss of concentration, memory defect and unwonted irritability were noted by his relatives in this period.

In the terminal stages of the illness heart failure developed and he died of pulmonary œdema.

Necropsy.—The body was that of a well-built middle-aged man showing considerable sacral œdema. There was no abnormal pigmentation. The heart was enlarged,

XUM

weighing 500 grammes; the left and right ventricles were both hypertrophied and dilated. The myocardium showed "thrush-breast" striations. The larger blood vessels showed minimal atheroma. Both the lungs weighed just under 1,000 grammes and were markedly œdematous. The alimentary tract was normal. The liver showed a fairly severe degree of centrilobular venous congestion. The pancreas, adrenals and kidneys were normal. The spleen weighed 110 grammes and contained several fibrous nodules, the largest being 1 cm. in diameter. The cervical and the para-aortic lymph nodes were enlarged to 2 cm. in diameter and were firm and fibrous. The marrow from the sternum showed no evidence of hæmopoiesis.

Histologically the lymph nodes and splenic nodules consisted for the most part of collagenous fibrous tissue with a few remaining cellular areas of Hodgkin's tissue. The heart muscle showed fatty change of the fibres.

Nervous system: macroscopically the brain and its dura and leptomeninges were normal. The spinal cord appeared normal on external examination and nowhere was the dura thickened or at all compressed. The arachnoid of the thoracic cord appeared a little thickened over the anterior surface. Histologically no abnormality was found in the brain. Sections of the spinal cord showed a severe degree of myelomalacia in the regions of T.4 and T.5. There was old diffuse vacuolation of the peripheral zones of all columns, most particularly in the anterior and lateral columns. A more recent lesion was practically confined to the dorsal columns and the corticospinal tracts of the lateral columns (fig. 8). Here the changes consisted of a breakdown of myelin sheaths with active astrocytic gliosis. There were accumulations of swollen microglial cells. In places the lesion was patchy and had a perivascular distribution (fig. 9). Here the myelin sheaths more distant from the vessels were spared, but for the most part the individual foci had coalesced. There was marked astrocytic gliosis in this region but no general inflammatory cell reaction. There was some loss of neurones from the grey matter, though the remaining cells appeared to be quite healthy. The arachnoid, particularly over the anterior and lateral columns was thickened. No arterial or hyaline arteriolar lesions, such as have been described in cases of acute necrotic myelopathy by Greenfield and Turner (1939) were found. There were no venous thromboses or varicosities. Above and below the affected segments ascending and descending tract degenerations were present.

The lesions in the central nervous system in this patient do not really closely resemble those of any known vitamin deficiency. They resemble to some extent those of subacute combined degeneration of the cord, particularly where the foci appear to commence in relationship to a small vessel, later spreading to form large demyelinated areas. However, the definite localization of the lesions to two thoracic segments, at this late stage of the disease, suggests rather a vascular or compressive lesion. Careful examination with these ideas in mind revealed no such lesions. It may have been that deposits of Hodgkin's tissue within the vertebral cord had at some stage compressed the cord and that treatment with nitrogen mustards had caused complete dissolution of the tumour tissue. That this should occur without any significant residual fibrosis, such as is found in Hodgkin's lesions elsewhere is difficult to accept. The blood supply to the lower cord via the lumbar arteries may have been embarrassed by the large chain of para-aortic nodes compressing the lumbar arterial branches at their origins. This would diminish the total

XUM

blood flow to the spinal cord but does not explain why the fourth and fifth thoracic segments should be selectively damaged. Of interest in this connexion are the lesions in the thoracic cord described by Thomson (1956) in a case where dissecting aneurysm occluded the lumbar arteries. The lesions he described were predominantly in the grey matter and were not similar to the lesions in this case.

The heart weighed 500 grammes, the excess being due to hypertrophy of both the right and left ventricles. There is no adequate explanation of this in terms of either hypertension or pulmonary abnormality. This cardiomegaly is no doubt the response to the demand for a high cardiac output as the result of the long period of anæmia. It is not therefore necessary to regard the enlargement of the heart as part of a vitamin-B deficiency.

(6) Lesions of the Peripheral Nerves

Enlargement of lymph nodes may occasionally give rise to signs of local nerve compression. This was observed in 3 patients and in each the cause was obvious and the resulting paræsthesia mild.

Herpes zoster was noted in 4 patients; in 2 the eruptions were over the ophthalmic division of the fifth cranial nerve, in 2 others over the thoracic nerve roots. In none, as far as we could judge, was the appearance of the eruption an indication of local invasion of nerve roots by neoplastic tissue, nor did its appearance have the same sinister significance as the other neurological lesions in the reticuloses.

Alison and Gordon (1955) described one patient with Hodgkin's disease with clinical signs typical of the Guillain-Barré syndrome. At post-mortem widespread infiltration of the nerve roots by neoplastic cells was shown to be responsible for the signs, In the present series clinical signs of peripheral neuropathy were found in 4 patients. In 2 of these patients (Cases 5 and 29) the symptoms and the signs were typical of a severe peripheral neuropathy, and were associated with epilepsy, mental changes and papillœdema. In 2 patients the evidence of peripheral nerve involvement consisted of the loss of reflexes in one and sensory changes in the other, and in both the post-mortem examination showed loss of axons and myelin sheaths in the peripheral nerves. In summary, therefore, peripheral neuropathy may occur, though rarely, in the reticuloses and may accompany, as it did in 4 of our patients, other signs of involvement of the nervous system.

Discussion

The demonstration of neurological abnormalities in 45 of 229 patients suffering from a reticulosis serves to emphasize the frequency of these complications and supports the observations of previous authors. Two generalizations are to be made from this series. The first is that the

TABLE II.—Illustrates the Multiplicity, Time of Onset and Duration of Neurological Complications in 45 Patients Suffering from Reticuloses

Types of neurological involvement

TABLE II.—ILLUSTRATES THE MULTIPLICITY, TIME OF ONSET AND DURATION OF NEUROLOGICAL COMPLICATIONS IN 45 PATIENTS SUFFERING FROM RETICULOSES

Case No.	Type of reticulosis	Duration of reticulosis before C.N.S. involvement	Types of neurological involvement						Duration after C.N.S. involvement to death
			Mental	Fundi	Epilepsy	Focal intracranial lesion	Cord lesion	Peripheral nerve lesion	
1	Hodgkin's	7 yrs.	+	0	+	+	0	0	Alive 14 yrs.
2	,,	0 (–1 yr.)	+	+(P)	0	0	0	+(P.N.)	36 mths.
3	,,	18 mths.	+	+(P)(H)	0	0	0	0	3 wks.
4	,,	0 (– yr.)	+	+(P)	+	0	0	+(P.N.)	48 mths.
5	,,	1 yr.	0	0	0	+	+(D) T.7	+(P.N.)	13 mths.
6	,,	18 mths.	0	0	0	+	0	0	1 mth.
7	,,	18 mths.	0	+(H)	0	0	0	0	Alive 18 mths.
8	,,	2 yrs.	+	0	0	0	+(D) T.5	0	17 mths.
9	,,	4 yrs.	0	0	0	0	+(C) T.12	0	10 mths.
10	,,	1 yr.	+	+(H)	+	+	0	0	36 mths.
11	,,	6 yrs.	+	0	+	+	+(C) L.3–4	0	3 mths.
12	,,	2 yrs.	0	0	0	0	+(C) T.6	0	9 mths.
13	,,	1 yr.	0	+(H)	0	+	0	0	5 days
14	,,	1¼ yrs.	+	0	0	+	+(C) T.7	0	2 mths.
15	,,	0	0	0	0	0	+(C) T.8	0	24 mths.
16	,,	1¼ yrs.	+	+(H)	0	+	0	0	3 mths.
17	,,	0	0	0	0	0	+(C) T.4	0	18 mths.
18	,,	0	+	0	0	0	0	+H.Z.	12 mths.
19	,,	1	0	0	0	0	+(C) T.4	0	3 mths.
20	,,	1	0	0	0	0	+(C) T.4	0	3 mths.
21	,,	1	0	0	0	0	0	+Brachial plexus	8 mths.
22	,,	0	0	+(H)	0	0	0	0	6 mths.
23	,,	6 yrs.	0	+(P)	0	0	0	+Brachial plexus	Alive 15 mths.
24	,,	2 yrs.	0	0	0	0	0	+H.Z.	Alive 24 mths.
25	,,	1 yr.	+	+(H)	0	0	0	0	6 mths.
26	,,	0	0	0	0	0	+(C) T.7	0	4 mths.
27	,,	3 yrs.	+	0	0	0	+(C) T.7	0	Unknown
28	,,	3 yrs.	0	0	0	0	0	+H.Z.	Unknown
29	,,	4 yrs.	+	+(P)	0	0	+(?D) T.4	+(P.N.)	3 mths.
30	,,	0 (–9 mths.)	0	0	0	0	+(?D) T.4	0	Alive 22 mths.
31	,,	8 mths.	+	0	0	0	0	0	2 mths.
32	,,	0 (–6 mths.)	0	0	0	0	+(C) T.3	0	Alive 3 mths.
33	Reticulosarcoma	2 mths.	0	+	0	0	0	0	3 wks.
34	,,	0	0	+ direct	0	0	+(C) T.2–C.6	0	4 mths.
35	,,	0	0	+(H)	0	+	0	0	10 days
36	,,	4 mths.	+	0	0	0	0	0	3 yrs.
37	,,	0	0	+(H)	0	0	0	0	6 mths.
38	,,	0	0	0	0	+	+(C)C.equinaL3	0	5 mths.
39	,,	6 mths.	0	+(P)	0	0	+(C) L3	+Brachial plexus	6 mths.
40	,,	1 mth.	0	0	0	+	+(C) T.3–6	0	2 mths.
41	,,	0	0	0	0	0	+(C) T.2–L.4	0	7 mths.
42	Lymphosarcoma	1 mth.	+	+(P)	+	0	+(?D) T.7	0	Alive 24 mths.
43	,,	4 yrs.	0	0	0	0	0	+H.Z.	Alive 10 mths.
44	,,	2 yrs.	+	0	0	+	0	0	6 mths.
45	Follicular lymphoreticulosis (Brill-Symmers)	15 yrs.	0	0	0	+	0	0	Unknown

* = C.N.S. involvement preceded reticulosis (duration in brackets). P = Papillœdema. H = Retinal hæmorrhage. D = Degeneration.
C = Compression. P.N. = Peripheral neuropathy. H.Z. = Herpes Zoster.

development of neurological abnormalities is not confined to any particular variety of reticulosis. The second is that the appearance of neurological signs is usually an indication that the disease is about to advance rapidly, or, if the first intimation of the reticulosis is the development of neurological signs, that the disease will probably then run a rapid course. This latter observation is subject to exceptions; local nerve compression and herpes zoster are the most important of these.

The type of the reticulosis, the site and nature of the neurological lesion, and the time-relationship of the onset of the neurological abnormality in the course of the reticulosis is shown in Table II. Two points of interest emerge. The first we have mentioned above; namely that there is no single pattern of neurological involvement typical of an individual reticulosis. The second is that direct invasion or compression of the nervous system by the reticular tissue, contrary to what might be expected from a study of the literature, was known to be responsible for the signs in only 21 of the 45 patients. In 16 of these patients the site of invasion or compression was the spinal dura or epidural space; in 2 others the optic nerve was involved by direct spread from adjacent deposits. In the remaining patients either hæmorrhage or "degenerative" changes were responsible for the signs. In 6 cases of dementia where necropsies were done no adequate pathological cause was found.

Spontaneous hæmorrhage, either into the retina or the brain, was the ætiological factor in 19 patients. This figure is surprisingly high. We found evidence in all of these patients of a blood dyscrasia sufficient for us to believe that a fall in the circulating platelets was the mechanism responsible.

After consideration both of the patients with direct invasion and of those developing spontaneous hæmorrhages, there remain 20 patients where certain of the signs could not reasonably be attributed to these causes.—7 had mental changes, 3 spinal cord lesions, and 3 peripheral neuropathy.

Some of these patients in the advanced stages of a reticulosis showed certain signs and complained of certain symptoms which, in another context, would have been highly suggestive of vitamin-B deficiency. Pigmentation of the skin, peculiarly severe dysæsthesia of the feet, mental changes and a mode of death not unlike Wernicke's encephalopathy were the most important of these. As a direct result of this the level of the blood pyruvate was estimated in a number of these patients. The results are expressed in Table III.

From this table it will be seen that in 6 of the patients with mental changes, 5 with abnormal appearances of the optic disc, in 3 with peripheral neuropathy and in 8 of the patients with spinal cord lesions, the blood pyruvate was elevated. There has not been a sufficient opportunity to observe when the abnormality develops and its relationship to the

TABLE III.—ILLUSTRATES THE NEUROLOGICAL SIGNS IN 11 PATIENTS WITH A RETICULOSIS, IN WHOM THE BLOOD PYRUVATE LEVELS WERE RECORDED AND FOUND TO BE ABNORMAL.

Type	*Case No.*	*Neurological abnormality*	*Blood pyruvate level mg. highest level per 100 ml.*
Hodgkin's	8	Mental. Cord lesion (D)	1·6*
Hodgkin's	31	Mental	3·9
Hodgkin's	5	Cord (D). Focal intracranial. Periph. neuritis	1·1
Hodgkin's	4	Mental. Papillœdema. Epilepsy. Periph. neuritis	1·6
Hodgkin's	3	Mental. Papillœdema. Retinal hæmorrhage	4·9
Hodgkin's	30	Cord lesion (D)	1·8*
Hodgkin's	29	Mental. Papillœdema. Cord (D). P.N.	2·9
Reticulosarcoma	39	Papillœdema. Cord (C). Brachial plexus compression	1·2*
Reticulosarcoma	40	Focal intracranial lesion. Cord (C) ..	2·2*
Reticulosarcoma	41	Cord (C)	2·8*
Lymphosarcoma	42	Mental. Papillœdema. Epilepsy. Cord (?)	1·3*

*Returned to normal with vitamin-B therapy. D = Degenerative cord lesion. C = Compressive cord lesion.

onset of neurological signs. In one of the 2 patients (Case 30) where this was possible, we are not yet certain whether the cord lesion which developed some eighteen months before the rise in the pyruvate occurred was due to compression or to degeneration within the cord. Although we do not know at what stage the elevation of blood pyruvate appears, we can say that in the early cases of reticulosis which have been studied (12 patients) no patient has shown any rise in the blood pyruvate, and in the later stages patients who have shown this abnormality have always had a demonstrable neurological lesion of one type or another.

We have found no satisfactory cause for the abnormality of pyruvate metabolism. Dietetic deficiency, anæmia, renal or hepatic failure or treatment with nitrogen mustard and other forms of chemotherapy were not constantly present and we have no evidence of obstruction of the absorptive pathways. In 10 patients large doses of vitamin-B compound were given and in 6 of these there was a reversion to normal of the blood pyruvate. This observation suggests that in the advanced stages of the reticuloses there is either an increased demand for vitamin B by growing cells or there is a "block" in the carbohydrate cycle at the pyruvate level which can be overcome in some cases by giving large doses of the vitamin-B group. However, neither of these suggestions really provides a satisfactory explanation of the abnormality.

In certain of these patients histological studies showed changes in the nervous system similar to that described in various states of vitamin-B deficiency. In Case 2 and Case 5 a peripheral neuropathy without local compression or vascular cause was found. Another patient (Case 3)

XUM

showed foci of capillary endothelial changes in the brain similar to the lesions in Wernicke's encephalopathy—though the anatomical distribution was quite atypical. In Case 8 the focus of myelomalacia is similar to the "infectious myelitis" reported by Weil (1931) and to lesions referred to as acute necrotic myelopathy by Moersch and Kernohan (1934) and by Jaffe and Freeman (1943) who found an association with malignant neoplasm outside the nervous system. In spite of these similarities in the pathology to vitamin-B deficiencies we must emphasize that there has been no clear clinical response to treatment with vitamin-B compound. Patients with dementia of the type described in Case 3, died either before treatment was given or before a reasonable time had elapsed after treatment.

In 2 cases with early fundal changes we felt that treatment was responsible for the clinical improvement that occurred but we do not know sufficient of the possible natural variations in this type of lesion to exclude the possibility that the improvement was spontaneous. Finally in one patient with peripheral neuropathy no improvement followed treatment with vitamin B (Case 4); in a second patient (Case 8), it was not surprising that there was no improvement even though the blood pyruvate returned to normal when the histological appearance of the cord (fig. 8) was revealed.

In spite of the inconclusive evidence of a reversible metabolic change in the reticuloses due to a "conditioned" vitamin-B deficiency, experience with another patient has given some support to this belief. A female patient of 40 years who for ten years was known to have a large neoplastic abdominal mass was admitted with epilepsy, personality change, appearances resembling "papillœdema" and 2 st. loss in weight despite normal diet. Two attempts at biopsy had previously failed due to circulatory collapse at operation. The only abnormality in the investigations was a blood pyruvate level of 3·9 mg. per 100 ml. (The C.S.F. resting pressure and analysis were normal.) Treatment with vitamin-B compound was followed by disappearance of all her symptoms and signs with the exception of residual atrophy of the right optic disc and persistence of the abdominal mass. The blood pyruvate returned to normal three weeks after commencing treatment and has remained normal for twenty months. Anti-convulsant treatment is still being given as a precautionary measure.

During the last decade a steadily increasing literature has appeared on the subject of neurological lesions produced by visceral neoplasm without evidence of secondary deposits within the nervous system. Subacute cerebellar degeneration (Brain *et al.*, 1951), peripheral neuropathy (Denny-Brown, 1948), (Lennox and Pritchard, 1950) and myopathy (Henson *et al.*, 1954) have all been described. The pathogenesis of these changes within the nervous system has not yet been explained.

XUM

A raised blood pyruvate was noted in one patient by Henson *et al.* (1954) and in 2 patients by Heathfield and Williams (1954) though at the time they felt that the evidence for a vitamin-deficient state was not conclusive.

The cases we have described differ from the cases in the literature not only in their association with the reticuloses rather than with a carcinoma, but also in the type of neurological disorder produced. This statement is true at the moment but it is recognized that more experience with these lesions in Hodgkin's disease and the other reticuloses may demonstrate that they are yet another facet of a group of pathological lesions in the central nervous system which may be caused by a variety of systemic diseases.

We have drawn attention to the various mechanisms that can produce neurological signs in the reticuloses, the most important of these being, blood dyscrasia, local compression, and a degenerative lesion of "metabolic origin."

A combined clinical and pathological study of these cases has impressed upon us that more than one of these processes may be responsible for the production of neurological signs in the same patient. This is particularly noticeable in those cases with signs of cord compression, which can be due to compression of the spinal cord by neoplastic tissue, degenerative changes in the spinal cord not apparently related to involvement by neoplastic tissue, or, to a combination of both processes.

When neurological signs of cord involvement are due to both compression and degeneration, treatment with vitamin B may not have any appreciable influence on the neurological signs, and this has been our experience in several such cases.

Summary

(1) The nervous system was affected in 45 of 229 patients suffering from a reticulosis.

(2) The neurological abnormalities were as follows: spinal cord lesions in 21; mental changes in 17; changes in the optic fundus in 17; focal intracranial lesions in 13; lesions of the peripheral nerves in 11; epilepsy in 5.

(3) Neurological signs were attributable to direct invasion or compression by neoplastic tissue (21 cases); to spontaneous hæmorrhage following thrombocytopenia (19 cases); and to a degenerative change, often accompanied by a raised blood pyruvate (20 cases). In several patients more than one of these factors was responsible for the neurological signs.

(4) Papillœdema, not accompanied by raised intracranial pressure, was noted in 7 patients.

XUM

(5) In the degenerative group, other symptoms and signs of vitamin-B deficiency were present and the elevation of the blood pyruvate regressed after treatment with vitamin B.

We wish to thank Professor A. C. P. Campbell, Dr. Fergus R. Ferguson, Dr. J. F. Wilkinson, Dr. M. C. G. Israëls and Mr. R. T. Johnson for permission to study cases under their care and for valuable criticism and reading the manuscript.

REFERENCES

ALLEN, I. M., and MERCER, J. O. (1936) *J. Neurol. Psychopathol.*, **17,** 1.
ALLINSON, R. S., and GORDON, D. S. (1955) *Lancet*, **2,** 120.
BRAIN, W. R., DANIEL, P. M., and GREENFIELD, J. G. (1951) *J. Neurol. Neurosurg. Psychiat.*, **14,** 59.
CAMPBELL, A. C. P., and BIGGART, J. H. (1939) *J. Path. Bact.*, **48,** 245.
DENNY-BROWN, D. (1948) *J. Neurol. Neurosurg. Psychiat.*, **11,** 73.
EAST, C. F. T., and LIGHTWOOD, R. C. (1927) *Lancet*, **2,** 807.
FORREST, D. (1927) *Lancet*, **2,** 809.
GREENFIELD, J. G., and TURNER, J. W. A. (1939) *Brain*, **62,** 227.
HEATHFIELD, K. W. G., and WILLIAMS, J. R. B. (1954) *Brain*, **77,** 122.
HENSON, R. A., RUSSELL, D. S., and WILKINSON, M. (1954) *Brain*, **77,** 82.
JACKSON, H., Jr., and PARKER, F., Jr. (1945) *New Engl. J. Med.*, **233,** 369.
JAFFE, D., and FREEMAN, W. (1943) *Arch. Neurol. Psychiat., Chicago*, **49,** 683.
LENNOX, B., and PRITCHARD, S. (1950) *Quart. J. Med.*, **19,** 97,
MOERSCH, F. P., and KERNOHAN, J. W. (1934) *Arch. Neurol. Psychiat., Chicago*, **31, 504.**
SPARLING, H. J., Jr., ADAMS, R. D., and PARKER, F., Jr. (1947) *Medicine, Baltimore*, **26,** 285.
THOMPSON, G. B. (1956) *Brain*, **79,** 111.
WEBER, F. PARKES (1923) *Quart. J. Med.*, **17,** 1.
WEIL, A. (1931) *Arch. Neurol. Psychiat., Chicago*, **26,** 1009.
WINKELMAN, N. W., and MOORE, M. T. (1941) *Arch. Neurol. Psychiat., Chicago*, **45,** 304.

XUM

XUM

PLATE V

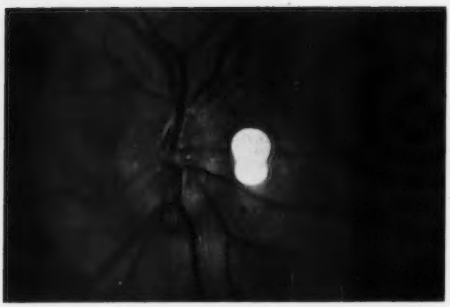


FIG. 1.

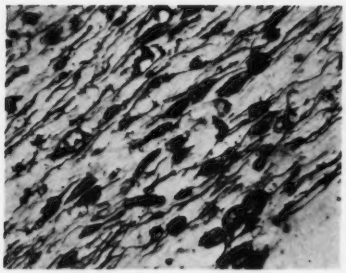


FIG. 2.

FIG. 1.—Retinal photograph showing œdema of the left optic nerve head. Case 2.

FIG. 2.—Axons in optic chiasma showing "torpedo" swellings and end-bulbs. ×500. Gros-Bielschowsky. Case 2.

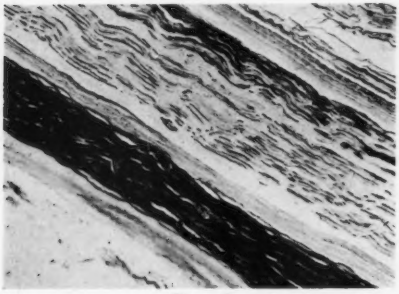


FIG. 3.

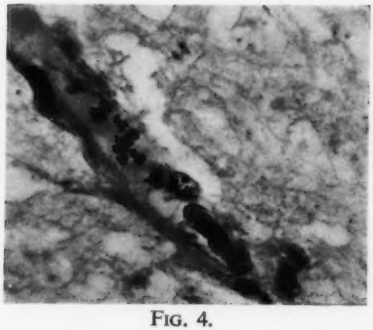


FIG. 4.

FIG. 3.—Two nerve fibre bundles from lateral popliteal nerve. The lower is normally myelinated, the upper shows marked loss of myelin sheaths. ×60. Methasol fast blue stain for myelin. Case 2.

FIG. 4.—Capillary from area of hæmorrhages showing swollen endothelium and mitotic figure in endothelial cell. ×600. Hæmatoxylin and eosin. Case 3.

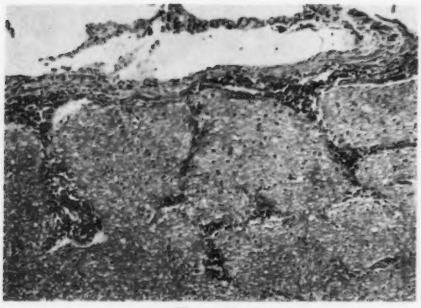


FIG. 5.

FIG. 6.

FIG. 5.—Longitudinal section of optic nerve. The nerve sheath and perivascular spaces within the nerve are infiltrated with reticulum cells. ×110. Hæmatoxylin and eosin. Case 33.

FIG. 6.—Section of œdematous optic nerve head. ×15. Case 33.

To illustrate article by E. C. Hutchinson, B. J. Leonard, C. Maudsley and P. O. Yates.

XUM

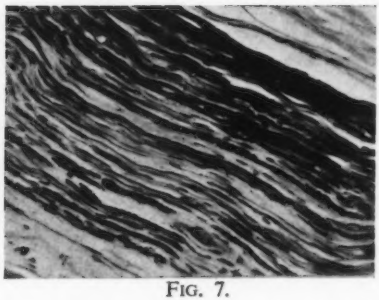


FIG. 7.

FIG. 8.

FIG. 7.—Small nerve bundle from sural nerve. There is fairly marked loss of myelin sheaths. ×200. Methasol fast blue stain for myelin. Case 5.

FIG. 8.—Section of upper thoracic spinal cord. There is considerable demyelination of dorsal and lateral columns. The periphery of all columns shows diffuse vacuolation. Methasol fast blue stain for myelin. Case 8.

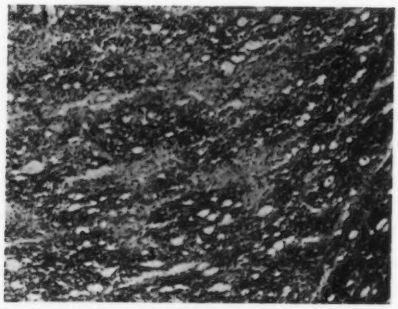


FIG. 9.—High power of lateral column from fig. 8. There is an extensive patchy demyelination with islands of myelin sheaths remaining relatively intact. ×75. Methasol fast blue stain for myelin. Case 8.

To illustrate article by E. C. Hutchinson, B. J. Leonard, C. Maudsley and P. O. Yates.

XUM

XUM

PROGRESSIVE MULTIFOCAL LEUKO-ENCEPHALOPATHY

A Hitherto Unrecognized Complication of Chronic Lymphatic Leukæmia and Hodgkin's Disease[1]

BY

KARL-ERIK ÅSTRÖM,[2] ELLIOTT L. MANCALL
AND EDWARD P. RICHARDSON, JR.

(From the Departments of Neurology-Neuropathology and of Pathology, Harvard Medical School, and the Neurology Service and the Neuropathology Laboratory, Department of Pathology, Massachusetts General Hospital, Boston)

Introduction

A number of pathological studies have elucidated the various ways in which leukæmia and malignant lymphoma may affect the central nervous system. The most common complications of *leukæmia* are brain hæmorrhages and accumulations of leukæmic cells in the meninges and brain (Diamond, 1934; Schwab and Weiss, 1935; Leidler and Russell, 1945; Parker, Sparling and Adams, 1947, and others). In addition, leukæmic cells may infiltrate cranial and spinal nerves and accumulate in the epidural space with resultant cord ischæmia (cf. Fried, 1926). Small scattered areas of softening in the spinal cord have been reported by Nonne (1897), Critchley and Greenfield (1930) and others. According to the latter authors such foci represent an early and partial form of the myelomalacia which is commonly found in leukæmic cases.

The neurological complications of *Hodgkin's disease* have been the subject of several comprehensive reports (*see* e.g. Ginsburg, 1927; Eugénis, 1929; Weil, 1931; Viets and Hunter, 1933; von Hagen, 1937; Goldman, 1940; Jackson and Parker, 1945; Sparling, Parker and Adams, 1947). The most common complication is spinal cord compression by epidural masses which originate by spread directly from adjacent vertebræ or through the intravertebral foramina from mediastinal and retroperitoneal lymphatic tissue. Lymphomatous tissue may similarly extend from cervical nodes or lymphoid tissue in the nasopharynx to the bones of the base of the skull and into the posterior fossa with involvement of cranial nerves. On a cytological basis Jackson and Parker (1944) distinguish between Hodgkin's granuloma and Hodgkin's sarcoma. Although

[1]This work was supported in part by the Harrington Fund.

[2]Research Fellow, Swedish Medical Research Council; present address: Department of Neurology, Serafimerlasarettet, Stockholm, Sweden.

XUM

Sparling, Adams and Parker (1947) were unable to record a proven case of Hodgkin's granuloma occurring either primarily or secondarily in the substance of the brain with the possible exception of that described by von Hecker and Fischer (1922), a case recently reported by Schricker and Smith (1955) clearly appears to represent primary intracerebral Hodgkin's granuloma. It is well known that Hodgkin's sarcoma may arise primarily in the brain parenchyma as first shown by Sparling and Adams (1946).

Other neurological complications of Hodgkin's disease are rare. Rottino and Hoffman (1950) describe a case of Hodgkin's disease with granulomatous tissue in the Virchow-Robin spaces which was thought to resemble sarcoid. Shapiro (1930) described one case of Hodgkin's disease with tract degeneration in the spinal cord without demonstrable epidural masses. He therefore postulated the existence of a blood-borne toxin in Hodgkin's disease which could act upon the nervous system. This hypothesis has never been confirmed by the observations of others (cf. Weil, 1931).

Recently we have had the opportunity to study two cases of lymphatic leukæmia and one of Hodgkin's disease with widespread lesions in the central nervous system. Since the affection bears no resemblance to any hitherto recognized complication of these diseases, we feel justified in presenting a description of our findings and in calling attention to the unique nature of this neuropathological disorder.

Case 1.—L. C. (MGH 17258).

A 71-year-old seamstress with chronic lymphatic leukæmia developed a rapidly progressive neurological disease with death within four months. Post-mortem examination demonstrated a widespread demyelinative process throughout the cerebral hemispheres.

In 1937, on a routine examination, the patient was discovered to have lymphatic leukæmia; at that time the white blood cell count was 28,000 per c.mm. with a differential count of 47 per cent polymorphonuclear neutrophils, 49 per cent lymphocytes, 3 per cent monocytes, and 1 per cent eosinophils. The hæmoglobin was 85 per cent, the red blood cell count 4·78 million per c.mm., the ESR 52 mm. in one hour. No specific therapy was given, and the patient was well for the next twelve years. In 1949, enlargement of the liver and spleen was first described. The white blood cell count was then 24,000 with 82 per cent lymphocytes. The patient was given radiotherapy to the liver (total 300 r in air). In 1951, she developed a severe hæmolytic anæmia during which the hæmoglobin fell to 3·0 grammes per 100 ml. and the white blood cell count rose to 147,000 with 90 per cent lymphocytes. A pleural effusion appeared; the aspirated fluid contained 1,600 lymphocytes per c.mm. She was treated with blood transfusions, ACTH, and radiotherapy to the spleen (total 550 r in air) with gradual improvement in her general condition and in the hæmatologic findings.

In November 1952 she became aware of gradually developing left-sided weakness several weeks after a minor fall. Examination on November 10, 1952, demonstrated diffuse weakness and ataxia of the left leg and inequality of the knee-jerks, the left being brisker than the right. A lumbar puncture gave clear, colourless cerebrospinal fluid under a pressure of 120 mm. of water, with no cells and a protein content of 30 mg. per 100 ml.

She was admitted to the Massachusetts General Hospital on November 26, 1952,

XUM

because of increasing weakness. On examination the blood pressure was 110/60, pulse 72, respirations 20, and temperature 99·0° F. There was no significant lymphadenopathy. The heart and lungs were normal. The liver and spleen were moderately enlarged. The mental state was normal. Cranial nerve function was normal, as were the optic fundi. There was no visual field defect. In addition to the weakness of the left leg there was profound proximal weakness of the left arm without facial weakness. The tendon reflexes on the left were generally brisker than those on the right, and the left plantar reflex was extensor. There were no sensory abnormalities. The lumbar puncture was repeated, with findings similar in all details to those previously noted. A course of radiotherapy was directed to the right side of the head (total 800 r in air) without improvement.

She was readmitted to the hospital on February 28, 1953, because of restlessness, disorientation, increasing weakness, nausea, vomiting, and urinary and fæcal incontinence. Pertinent findings now included intermittent disorientation, paralysis of conjugate gaze to the left, and a severe left hemiparesis involving the face. Lumbar puncture gave clear cerebrospinal fluid under a pressure of 60 mm. of water; the fluid contained 1 lymphocyte per c.mm. and a protein of 22 mg. per 100 ml. Radiographs of the skull were normal. An electroencephalogram was grossly abnormal, with diffuse slow activity in the theta range and rare delta activity; in addition, areas of flattening and occasional sharp waves were present on the right.

The patient's condition worsened rapidly. She became mildly confused and developed slurred speech. Visual disturbance became more marked, with impairment of upward gaze and gaze to the right, and she became totally blind. Hypalgesia appeared over the left side of the face, and the left corneal reflex was diminished. Swallowing became impossible. The gag reflex was diminished and palatal movements were weak, particularly on the left. The left hemiplegia became more profound and right-sided weakness developed. All tendon reflexes were lost except for the left biceps and knee jerks. The left plantar reflex remained extensor, the right flexor. Lumbar puncture demonstrated clear cerebrospinal fluid under a pressure of 155 mm. of water; the fluid contained 25 lymphocytes per c.mm. and a protein of 22 mg. per 100 ml. Stupor ensued, signs of pulmonary congestion appeared, and the patient died on March 19, 1956, approximately four months after the onset of the neurologic disorder.

Pathological findings (*MGH autopsy No.* 16159).—General: The autopsy was performed fourteen hours post mortem. The trachea and bronchi contained yellow-green foamy exudate. The lungs weighed 750 grammes, and showed basal atelectasis and congestion. The heart weighed 200 grammes and appeared grossly normal. The liver weighed 1,300 grammes and the spleen 250 grammes. Microscopically there was evidence of slight myocardial fibrosis, and bronchopneumonia. Sections of lymph nodes revealed loss of normal architecture with absence of germinal centres, numerous foci of dense lymphocytic infiltration, and evidence of extramedullary hæmatopoiesis. The bone-marrow was diffusely infiltrated with lymphocytes; in some areas this infiltration was so dense that no bone-marrow elements were seen.

Neuropathological findings.—The brain weighed 1,350 grammes in the fresh state. There were no significant external abnormalities except for palpable fluctuation over the right parietal region, and a minimal degree of atherosclerosis. Multiple horizontal sections of the cerebral hemispheres, brain-stem, and cerebellum after formalin fixation showed diffuse softening, granularity, and greyish discoloration of the white matter of the cerebrum. On the right side, this extended from the occipital lobe into the frontal lobe; on the left, it was confined to the occipital pole. In general the process extended to the cortex, although in some regions the arcuate fibres appeared to be preserved. The basal ganglia, brain-stem, and cerebellum were grossly normal. The spinal cord and peripheral nerves were not examined.

XUM

Representative celloidin-embedded sections of brain were stained with cresyl violet, hæmatoxylin and eosin, and according to Loyez' method for myelin. Representative frozen sections were stained with oil red O for neutral fats, and according to Cajal's reduced silver method for axis cylinders, Cajal's gold sublimate method for astrocytes, Spielmeyer's method for myelin, and Holzer's method for glial fibrils.

On microscopical examination, the sections stained for myelin showed extensive loss of myelin sheaths in widespread areas in both cerebral hemispheres. In the right cerebral hemisphere there were two large lesions (fig. 1A). The more posterior one of these involved nearly the entire central white matter of the occipital and posterior parietal lobes except for some of the convolutional white matter medially. Laterally it extended to the cortical border, and for the most part included the subcortical and deep intracortical fibres. Its borders were in general sharply demarcated though somewhat irregular. The medial border of the lesion ran parallel to the geniculo-calcarine radiation, which was somewhat pale. Its anterior border was less sharply demarcated than that posteriorly, and was made up of a coalescence of numerous spherical or oval foci 0·5 mm. or less in diameter. Inferiorly it extended to the posterior horn of the lateral ventricle. The more anterior lesion was situated in the central and convolutional white matter of the frontal and Rolandic regions and was connected with the more posterior one by an ill-defined isthmus. The borders of this lesion were not sharp but were made up of innumerable minute foci up to about 1·0 mm. in diameter. These foci occurred in increasing density toward the centre of the lesion, finally becoming confluent. Scattered isolated but similar foci of pallor of myelin staining were irregularly distributed at a considerable distance anterior to the large lesion. There was one discrete lesion, $1{\cdot}5 \times 2{\cdot}0$ mm., in the cortex of the middle frontal gyrus (fig. 1B).

In the left cerebral hemisphere there was a large lesion, about 3·0 cm. in length by 1·0 cm. in width, in the central white matter of the occipital lobe. This was clearly made up of a confluence of small foci (fig. 1C). As in the right hemisphere, there were very small isolated lesions scattered irregularly throughout the entire hemisphere, both in central white matter and in cortex.

No lesions were found in the basal nuclear masses, brain-stem, or cerebellum.

Under higher magnification, the lesions were not sharply outlined, but invariably had a narrow peripheral zone, which gradually blended with the surrounding normal tissue, in which there was partial loss of myelin sheaths together with abnormality in appearance of many of those remaining—irregular swellings and fragmentation (fig. 2A). Within the centre of the large lesions myelin sheaths were totally absent. In smaller lesions there were a few scattered intact myelin sheaths in the central portions; these were invariably fibres of extremely small calibre, whereas the larger fibres had disappeared. In the very smallest lesions there was decrease in number of myelin sheaths, with changes in those remaining similar to what was observed in the periphery of the large lesions. A considerable number of the small lesions were located around small blood vessels, although this relationship was not demonstrated in all.

In many of the regions where myelin sheaths were absent, axis-cylinders, as demonstrated by silver impregnation, were abundantly present, although not as numerous as in the intact portions of white matter. Many of the axons within these lesions were of normal appearance, whereas some were irregularly thickened or terminated in rounded or club-like swellings (fig. 2C). In the very extensive lesion in the right occipito-parietal region there was severe, but not total loss of axons.

In sections stained for neutral fats, most lesions contained large numbers of phagocytic cells filled with brightly red-staining sudanophilic intracytoplasmic droplets (fig. 2B). In the smallest lesions neutral fat was absent. At the periphery of lesions in which the centre contained abundant intensely sudanophilic material, there were

XUM

phagocytic cells in which there were fine droplets in the cytoplasm that were only very faintly sudanophilic. This peripheral region corresponded to the zone of incomplete loss of myelin sheaths as seen in the sections stained for myelin in which the fine droplets in the cytoplasm of the phagocytic cells were of the same colour as the myelin.

Cell stains showed that the lesions typically were densely cellular. Within the centre there were varying numbers of rounded phagocytic cells with vacuolated cytoplasm, corresponding to the fat-filled cells demonstrated by oil red 0 staining. Throughout such lesions were considerable numbers of plump astrocytes which, in the central regions of the lesions, often formed a dense feltwork of glia fibrils that was well shown by the Holzer method. The peripheral portions of the lesions were more densely cellular than the centres and contained closely aggregated astrocytes, pleomorphic microglial cells, and fully developed phagocytes. Associated with the largest lesions, and most numerous in the peripheral portions, were thick collections of closely packed lymphocytes in the perivascular spaces.

In addition to the cells noted above, a number of cells of very unusual type were encountered. Firstly, scattered within the larger lesions there were very large cells with oval or irregular nuclei measuring up to $24 \times 40\,\mu$, that contained densely staining large masses of chromatin. (In comparison, the nuclei of the large reacting astrocytes measured generally about $9 \times 17\,\mu$.) These cells had abundant cytoplasm (pale violet with cresyl violet, pink with hæmatoxylin and eosin) and frequently had stellate processes identical to those of astrocytes (fig. 2D). Occasionally these cells were binucleated or multinucleated.

Unequivocal mitotic figures were found in some of these giant cells. The mitoses at times were atypical, being either multipolar (fig. 3A, B) or multiple (fig. 3C). The cells showing mitotic figures had generally rounded cell bodies and did not show distinct processes, but because of their enormous size and similarity in other respects were considered to be identical with the giant cells with processes already mentioned.

Secondly, in the periphery of the lesions there were scattered but numerous cells with spherical or slightly oval densely basophilic nuclei in which individual chromatin particles generally were indistinguishable. In numerous examples of such cells the nucleus contained indefinitely outlined eosinophilic inclusion material associated with marginal location of basophilic chromatin (fig. 5B). These nuclei were surrounded either by a thin rim of cytoplasm without distinguishable processes visualized in any of the staining methods used, or by clear haloes. The smallest examples of these densely basophilic nuclei were slightly larger than the normal oligodendrocyte nuclei seen in intact portions of the white matter ($7\,\mu$ as compared with 4 to $5\,\mu$); the largest nuclei were approximately the size of the nucleus of a large reacting astrocyte (about $13\,\mu$). Every degree in size between these extremes was demonstrable. When these cells were situated in a longitudinally oriented bundle of fibres adjacent to the edge of a large lesion, as in the right geniculo-calcarine radiation, these basophilic nuclei were found in rows like the normal interfascicular oligodendrocytes, and transition forms between normal oligodendrocytes and these darkly staining cells could be identified. Furthermore, some of the interfascicular rows of nuclei in such regions were made up partly of normal oligodendrocytes and partly of the large darkly staining cells (fig. 6B).

Depending upon the size of the lesion, there were varying numbers and kinds of cells. The smallest identifiable lesions consisted of a minute cluster, some 40–50 μ in diameter, of activated microglial cells, without astrocytic hyperplasia, generally situated around a thin-walled blood vessel of slightly larger than capillary size. No recognizable changes in the myelin could be seen.

In somewhat larger lesions, 150–200 μ in diameter, there was increase in size and number of astrocytes, along with fully developed phagocytes in addition to activated microglial cells; scattered densely basophilic nuclei of the type just described were likewise present. As already noted, typical lesions (i.e. those of about 400 to 800 μ in

XUM

size) were characterized by peripheral distribution of the most active glial proliferation and of the densely basophilic nuclei, whereas phagocytic cells were most numerous in the centre. The centres of the large confluent lesions, such as those encountered in the right parietal or frontal or left occipital regions, contained considerable numbers of the giant cells described above. Fat-laden phagocytes were present in abundance as were glial fibrils. At the periphery there frequently was a dense wall of glial proliferation containing many of the darkly basophilic round nuclei, activated microglia, fully developed phagocytes, and plump reacting astrocytes but no gigantic cells (fig. 5A). The centre of the extensive lesion in the right occipital lobe consisted almost entirely of astrocytes, glial fibrils, and phagocytic cells in varying numbers; in some regions the phagocytic cells were almost absent except for aggregates of them in the perivascular spaces; in others, they were scattered in considerable numbers throughout the tissue. The giant cells were most numerous in the regions where astrocytes, glial fibrils, and phagocytic cells were intermingled, whereas they were not frequent in the parts characterized by fibrous gliosis alone.

Oligodendrocytes were absent within the centre of all but the smallest lesions. In the periphery where the glial reaction was most pronounced, and in a very narrow zone immediately outside, normal oligodendrocytes were reduced in number, whereas they were present in expected numbers in the intact tissue beyond.

The general architecture of the cerebral cortex was well preserved, although here and there throughout the cortex there were typical "senile plaques," and a number of nerve cells showed Alzheimer's neurofibrillary change. There were numerous reactive astrocytes and pleomorphic or rod-shaped microglial cells in portions of the cerebral cortex involved by the lesions. The round densely basophilic nuclei were encountered in varying numbers. Nerve cells within the lesions frequently appeared shrunken and pale, but in general showed little alteration even in areas which showed pronounced reactive glial changes. There were occasional nerve cells within or adjacent to lesions which presented a swollen rounded appearance suggesting axonal reaction. Other grey-matter structures of the cerebral hemispheres, brain-stem, and cerebellum were intact.

Except for scattered small collections of lymphocytes in the subarachnoid space, there was no evidence of disease of the meninges, nor was there any abnormality of the walls of meningeal or parenchymatous blood vessels. There were large collections of lymphocytes within the lumen of many vessels in no particular relationship to lesions. The ependymal surfaces of the ventricles were normal.

Case 2.—F. R. (MGH 912138)

A 73-year-old female accountant with chronic lymphatic leukæmia developed rapidly progressing neurological symptoms and signs and died within four months of their appearance. Post-mortem examination demonstrated widespread demyelinative lesions throughout the brain.

In June 1951 a diagnosis of chronic lymphatic leukæmia was established at the New England Deaconess Hospital, Boston, Mass. At that time the white blood cell count was 162,000 with 16 per cent polymorphonuclears, 60 per cent mature lymphocytes, 19 per cent immature lymphocytes, and 5 per cent monocytes. Hæmoglobin was 12·2 grammes per 100 ml., platelets were decreased, and the bleeding time was prolonged. Sternal marrow aspiration confirmed the diagnosis. She received 120 r whole body radiation with subsequent fall in white blood cell count to 20,000 of which 59 per cent were lymphocytes. In 1954–55, though asymptomatic, the patient received three courses of radiotherapy to the trunk (total 440 r). In March 1956, she was given 15 mg. of triethylenemelamine, following which the total white blood cell count was said to be normal.

Very soon after receiving this drug the patient complained of nausea and vomiting,

XUM

dizziness, fatigue, and became excessively irritable. In June 1956 following blood transfusions for moderately severe anæmia, she became agitated, cried frequently, and described headaches, an inability to concentrate which interfered with her work, unsteadiness of gait, and clumsiness of her right hand. On July 8, 1956, she complained of double vision and of difficulty choosing the correct word while speaking. Neurological examination at that time demonstrated no abnormalities except for poor performance of simple mental arithmetic. Five days later she was observed to walk with a broad-based gait. Within the following week she rapidly became worse, so that she was confined to bed and unable to feed herself. Examination showed a right homonymous hemianopia, pronounced dysphagia, weakness of the right arm, and slightly more brisk tendon reflexes on the left side. She was admitted to the Massachusetts General Hospital on July 24, 1956.

On admission the blood pressure was 160/70, pulse 80, respirations 18, temperature 98·6° F. General physical examination was unremarkable. Neurological examination now demonstrated that she was confused and disoriented. Recent memory was faulty. She could read individual words but could not follow written commands, was unable to read consecutively, had difficulty in naming objects, and used incorrect words in conversation. Writing movements could be performed, but written material was illegible. Dyscalculia, right-left disorientation, and finger agnosia were present, as well as a right homonymous hemianopia and weakness of conjugate gaze to the right. There was slight resistance to passive movements of the right arm and leg, and slowness of movements of those limbs without apparent weakness. Tendon reflexes were depressed in the right leg, and the right plantar reflex was extensor. Sensory tests demonstrated only diminished position sense in the right foot.

Laboratory studies showed a hæmoglobin of 12·6 grammes per 100 ml., hæmatocrit 37·5 per cent, white blood cell count 16,600 with 79 per cent lymphocytes, reduced platelet count, and normal bleeding and clotting times. The blood Hinton test was negative. Radiographs of the skull were normal. An electroencephalogram showed delta and theta activity and phase reversal in the left posterior temporal area. Alpha activity was frequently reduced or absent on the left. A lumbar puncture gave clear colourless cerebrospinal fluid under a pressure of 110 mm. of water; the fluid contained no cells and a protein of 29 mg. per 100 ml.

The patient's neurological condition worsened. She developed increasing aphasia, diminished left corneal reflex, left abducens weakness, right-sided flaccid hemiparesis and hemihypæsthesia, loss of tendon reflexes in the legs, and urinary and fæcal incontinence. She eventually became completely blind, mentally dull, and lapsed into coma. Cheyne-Stokes respirations appeared shortly before the patient's death on August 21, 1956, approximately four months after the onset of neurological symptoms.

Pathological findings (*MGH autopsy No.* 19024).—General: The autopsy was performed sixteen hours post mortem. Several soft homogeneous lymph nodes were found in the retroperitoneal area. There were non-adherent clots within the secondary divisions of both pulmonary arteries. The heart was normal. There was severe atherosclerosis of the left circumflex artery and moderate atherosclerosis of the aorta. The liver weighed 1,400 grammes and was diffusely yellow. The spleen weighed 400 grammes and was uniformly purple with loss of Malpighian corpuscular architecture. Microscopically, there was diffuse infiltration of the alveolar walls of the lung with mature lymphocytes, and dense portal infiltrates of similar composition in the liver. In the spleen there was a diffuse increase of lymphocytes; Malpighian corpuscles were not seen. The bone-marrow exhibited diffuse intense infiltration with mature lymphocytes with decrease of all myeloid elements except for megakaryocytes. Within lymph nodes there were loose sheets of mature lymphocytes with a follicular arrangement.

Neuropathological findings.—The brain weighed 1,200 grammes in the fresh state.

XUM

There was a moderate degree of atherosclerosis of the large vessels at the base. Minimal frontal convolutional atrophy was evident.

Multiple coronal sections of the cerebral hemispheres and horizontal sections of the brain-stem and cerebellum were made after formalin fixation. There was moderate dilatation of the ventricular system involving the lateral and third ventricles, slightly more pronounced on the left side. A large number of small greyish translucent spherical foci 1–2 mm. in diameter were seen in almost all regions of the cerebral hemispheres. They were most numerous in the parietal and occipital lobes, to a greater extent on the left side than on the right and least evident in the temporal lobes. The lesions occurred primarily in the deep layers of the cortex and subjacent white matter, and appeared singly and in chains, clumps, and more or less confluent clusters. In addition, there was a large (1·4 cm. in diameter) focus of softening and greyish-yellow discoloration in the left parieto-occipital area immediately superior to the geniculo-calcarine radiation and dorsal and lateral to the occipital horn of the lateral ventricle. A large number of small round lesions gave a mottled appearance to the caudate nucleus, putamen, claustrum, and thalamus bilaterally, but more marked on the left. The left amygdala was similarly involved. No lesions were macroscopically apparent in the brain-stem or cerebellum. The spinal cord and peripheral nerves were not examined.

Representative celloidin-embedded sections of brain were stained with cresyl violet, hæmatoxylin and eosin, and according to Loyez' method for myelin. A similar set of paraffin-embedded sections were stained with cresyl violet, hæmatoxylin and eosin, and according to Heidenhain's method for myelin and Bodian's method for axis cylinders. Representative frozen sections were stained with oil red O for neutral fats, cresyl violet in 1 per cent acetic acid for metachromatic lipids, and according to Cajal's reduced silver method for axis-cylinders, Spielmeyer's method for myelin and Holzer's method for glial fibrils.

In sections stained for myelin the lesions had the same general appearance as in Case 1. However, with the exception of the large focus in the left parietal region, they occurred as an extensive sprinkling of small lesions rather than as coalescent areas of large diameter (fig. 7, A, B). Furthermore, there was extensive involvement of the cerebellum and brain-stem (fig. 7, C, D).

The microscopic details of individual lesions with respect to distribution and form of myelin breakdown were identical to those in Case 1. There was no significant metachromasia of the breakdown products. In this case likewise there was relative preservation of axis cylinders (fig. 8, A, B, C).

A series of lesions from the smallest foci to larger coalescent areas could be followed, and showed the same features as in Case 1 (fig. 9, A, B). The same varieties of cells were encountered as in Case 1—thus, in all but the smallest lesions, there were large numbers of the unusual cells with darkly basophilic nuclei (fig. 9B), which tended to occur most frequently in the periphery of the lesions. Where these cells were located amid parallel fibre bundles, transitions between them and oligodendrocytes were identified (fig. 6A). Occasionally these nuclei contained eosinophilic inclusions, as in Case 1. Giant cells occurred very infrequently, although a few of them were found in the largest lesions; some were multinucleated (fig. 4A), and occasionally the nuclei contained homogeneous inclusions (fig. 4B). No mitoses were found in these cells. Extensive perivascular lymphocytic infiltrations such as occurred frequently in Case 1 were for the most part absent, although a few were found.

The appearance of cortical nerve cells was similar to that in Case 1. In the cerebral cortex there were scattered "senile plaques" and cells affected with Alzheimer's neurofibrillary change. The caudate nucleus and putamen, which were extensively involved with lesions, contained very large numbers of reacting astrocytes and the darkly basophilic nuclei described. Where these cells were most numerous, the small

XUM

nerve cells were greatly reduced in number, whereas the large nerve cells were present in expected numbers. Many of the large nerve cells, however, were swollen and showed central chromatolysis and eccentricity of the nucleus suggesting axonal reaction. Nerve-cell loss was fairly extreme in the claustrum, which likewise was heavily involved with lesions. The thalamus in general showed good preservation of cellular architecture despite the presence of many lesions. In the cerebellum most of the granule cells were pyknotic or presented a smudged appearance, typical of "conglutination" (Ferraro and Morrison, 1928). The Purkinje cells were well preserved. Nuclear structures in the brain-stem showed no significant nerve-cell change although there were numerous typical lesions.

There were no abnormalities in the meninges or blood vessels. As in the first case, some of the blood vessels contained accumulations of leukæmic cells in the lumen.

Case 3.[1]—T. D. E. (Emory University Hospital No. 61-707-U)

This 42-year-old male executive, with an established diagnosis of Hodgkin's disease developed neurological signs suggesting an infiltrating intracranial process and died in less than three months. Post-mortem examination demonstrated scattered demyelinative lesions in both cerebral hemispheres.

The patient was admitted to the Emory University Hospital on October 10, 1953, because of progressive weakness. A diagnosis of Hodgkin's disease had previously been made on the basis of a cervical node biopsy and radiotherapy given. A right pleural effusion was found, and the patient given a course of nitrogen mustard. He was readmitted in April, May, and June 1954 with complaints of anorexia and recurring chest pain. Findings included persistent right pleural effusion, mediastinal and axillary adenopathy, and intermittent low-grade fever. He was treated with additional courses of nitrogen mustard and with triethylenemelamine, cortisone, deep radiotherapy to the axilla, and instillation of radioactive gold into the right pleural cavity.

He was admitted for the last time on August 20, 1954. During the preceding two months, aphasia and inco-ordination had developed. Examination demonstrated mental confusion, and weakness of the right arm and face. Laboratory studies disclosed anæmia and lymphopenia. Routine blood chemical determinations were normal. Radiographs of the skull were normal. Radiotherapy was given to the left temporal area to a total of 350 r, but weakness and confusion increased, and the patient died in coma on the eighth hospital day, approximately ten weeks after the onset of neurological symptoms.

Pathological findings (*Emory University Hospital No. A*-54-155; *Massachusetts General Hospital Neuropathology Laboratory No. X*-165).—General: Post-mortem examination was performed one hour after death. A large loculated effusion was found in the right hemithorax. The right lung was completely collapsed and had a very thickened nodular whitish pleural investment. A fibrous mass of lymph nodes involved most of the mediastinal structures. The stomach and duodenum were closely attached to a hard fibrous mass of retroperitoneal nodes and fibrous tissue, which also enveloped the pancreas and extended down the aorta to the common iliac arteries. The liver weighed 2,000 grammes, the spleen 200 grammes; both exhibited ill-defined red and grey mottled lesions throughout the parenchyma. Microscopically, both lungs were infiltrated with Reed-Sternberg cells, and plasma cells were seen in the alveoli. In addition, there was a thickening of the pleura with severe vascular changes

[1]For the clinical and general pathological findings in this case and for so kindly furnishing us with paraffin-embedded stained sections of the nervous system and blocks of brain tissue preserved in alcohol, we are greatly indebted to Dr. Walter H. Sheldon, Chief of the Department of Pathology, Emory University, Georgia, and to Dr. Heinz Bauer of the same department.

XUM

in the lungs characterized by endothelial hyperplasia, at times leading to complete occlusion, and infiltration of the walls of the blood vessels with inflammatory cells—all consistent with severe radiation effect. In the liver and the spleen, there was obliteration of the architecture by diffuse fibrosis and the parenchyma was infiltrated by plasma cells, Reed-Sternberg cells and occasional lymphocytes. In lymph-nodes there was extensive fibrosis and focal necrosis, with infiltration by lymphocytes, plasma cells, and Reed-Sternberg cells. The bone-marrow showed a striking reduction in hæmatopoietic elements, with small foci of myeloid elements, plasma cells, macrophages and Reed-Sternberg cells.

Neuropathological findings.—The brain weighed 1,300 grammes in the fresh state. There were no abnormalities noted on external examination. The brain was sectioned after formalin fixation. In several areas within the white matter of both cerebral hemispheres there were scattered foci of ill-defined softening with a pink granular appearance. These varied between 1 to 3 mm. in diameter. Their margins blended gradually with the surrounding white matter. These lesions were most prominent in the left parietal region. The basal ganglia showed no lesions. The spinal cord was grossly normal.

Representative paraffin-embedded sections stained with cresyl violet, hæmatoxylin and eosin, eosin–methylene-blue, phosphotungstic acid-hæmatoxylin and according to Heidenhain's method for myelin, Bodian's method for axis cylinders, and a standard silver impregnation method for reticular fibres were studied.

The microscopic findings corresponded in every respect with those in the previous two cases. The lesions tended to be isolated, or in small clusters rather than the large confluent foci encountered in the other cases (fig. 10A). The relative sparing of axis cylinders in the presence of severe myelin destruction was likewise a feature in this case. The cellular reaction in the lesions was likewise identical except that giant cells were rare (fig. 4C). Cells with round darkly basophilic nuclei were numerous; their peripheral arrangement around typical lesions and their occurrence as interfascicular rows of nuclei were exactly as seen in previous cases. There were no inflammatory infiltrates in the meninges or in the perivascular spaces. The blood vessels were normal. There were no definite abnormalities of nerve cells.

Serial hæmatoxylin and eosin sections were prepared of a block of cerebral cortex and convolutional white matter containing a large number of typical lesions. Several of these which could be followed in their entirety in the sections were studied and found invariably to have a perivascular arrangement, generally around a large capillary or small venule (fig. 10B).

Discussion

Pathological Process

In each of these 3 cases a basically identical pathological process was found, characterized by widely disseminated small generally oval perivascular foci of destruction of myelin sheaths, with relative sparing of axis cylinders. A continuous series of lesions could be observed, both with respect to size and cytological characteristics, suggesting progressive stages in the development of the pathological process. The smallest discernible lesions consisted of tiny perivascular collections of pleomorphic microglia without definable alteration of the myelin. As the lesions enlarged, pleomorphic microglia and fully developed phagocytic cells appeared in ever greater numbers, and there were hypertrophy and proliferation of astrocytes. At the same time, there appeared increasing numbers of cells with round densely basophilic nuclei. Along with

enlargement of the lesions, there was evidence of myelin sheath destruction, first apparent as a "shadow" phase with reduction in their numbers; in larger lesions, there was complete fragmentation and disappearance of sheaths. The breakdown products of the myelin sheaths were typically sudanophilic. In still larger lesions, the periphery was characterized by a densely cellular wall made up of large numbers of pleomorphic microglial cells, proliferating astrocytes, and the densely basophilic nuclei. Gigantic cells with hyperchromatic irregular or very bizarre nuclei appeared within the more central portions of these larger lesions among numerous macrophages and in a background of typical fibrous gliosis. In one case (Case 1), these giant cells clearly underwent mitotic division. Further enlargement of the lesions resulted in their becoming confluent with one another. Inflammatory changes were striking in Case 1, but virtually absent in the other two cases. Except in the first case, in which the lesions were confined to the cerebral hemispheres, the disease process affected all levels of the brain. The spinal cord was not available to us in any of the cases. Nerve cells were generally normal even where lesions involved grey matter structures. However, some degree of nerve-cell alteration and loss was present within the more extensive lesions. Typical "senile plaques" and Alzheimer neurofibrillary changes were present in Cases 1 and 2. Blood vessels were normal in all three cases.

It is clear from the preceding description that there is a continuously progressive increase in the size of the lesions, and a steady evolution in the severity of the myelin destruction and in the accompanying cytological changes. These findings can only be explained by a chronic disorder which progresses by the continuous addition of new lesions, and by aggravation of those already present. Certain features of this process are so unusual and striking as to warrant further consideration. One most remarkable finding in these cases is the discovery of cells with deeply staining basophilic round nuclei which appear at an early stage in the development of the lesions. These have either a thin rim of basophilic cytoplasm or a clear perinuclear halo, and no processes. The nuclei in the larger forms may be homogeneous or may contain irregular eosinophilic inclusions. The origin and nature of these cells is not clear. They have neither the appearance nor the expected distribution of hæmatogenous elements, nor can they be identified with histiocytes. The lack of processes excludes astrocytic origin. On the other hand, these cells occur strikingly within rows of interfascicular oligodendrocytes bordering some lesions, alternating with normal oligodendrocytes, which they closely resemble; they increase in both size and number as the lesion is approached. These observations suggest that these cells are altered oligodendrocytes of a type hitherto unrecognized in the neuropathological literature.

Another most interesting finding in association with fully developed lesions is the occurrence of gigantic cells, identifiable, because of their

XUM

form and location, as astrocytes, but of a size and appearance not ordinarily encountered in the glial reaction to destructive lesions of the brain. Not only are the nuclei of enormous size, hyperchromatic, and frequently irregular in shape, and often multiple, but a considerable number of them clearly show mitotic figures, some of which are multipolar and thus of an abnormal variety (Case 1). Although cells with similar features have been described in acute demyelinative lesions by Creutzfeldt (1923) and Peters (1935), astrocytes of this sort are ordinarily met with only in neoplastic processes. However, the basic neuropathological process in these cases is not one of neoplasia for these reasons: First, the lesions show no evidence of expansile growth in the sense of a tumour, and secondly, the earliest lesions are characterized by simple tissue destruction, with no astrocytic proliferation whatsoever. The giant astrocytes, on the other hand, are found only in what appears to be a relatively late stage in the development of the lesions, and their occurrence and distribution is typical of astrocytes reacting to a primarily destructive lesion of brain tissue. It therefore seems justified to assume that these giant cells represent astrocytes which have undergone an alteration that renders them morphologically indistinguishable from neoplastic cells.

As is apparent from the description of the lesions, the neuropathological process fulfils the commonly accepted criteria for a demyelinative disorder, in that there is destruction of myelin sheaths with relative sparing of axis cylinders, nerve cells, and supporting structures, and a generally perivascular distribution of multiple disseminated foci (Adams and Kubik, 1952). Furthermore, the myelin breakdown products are of the usual sudanophilic type. In these basic respects the disease closely resembles *multiple sclerosis*; however, the very large numbers of lesions of great variability in size, the relative absence of sharply demarcated borders (although some lesions clearly do have this character), the lack of any tendency to subependymal or subpial distribution, and the presence of large numbers of grey matter lesions, as well as the unusual cytologic features, make it difficult for these cases to be so classified. Although the large posteriorly situated lesion in Case 1 somewhat resembles *Schilder's disease*, the character and distribution of the demyelinative process in general are not at all consistent with that disorder. *Acute disseminated encephalomyelitis* of the post-infectious variety is excluded by the general absence of inflammatory cells and by the great variability in size and age of the lesions. The condition bears no resemblance to *subacute encephalitis* (Dawson, 1933, 1934; van Bogaert, 1945), despite the presence of intranuclear eosinophilic inclusions in some of the cells as previously noted. The presence of bizarre gigantic astrocytes may raise the question as to whether these cases represent "*glioblastomatous diffuse sclerosis*" as described by Einarson and Neel (1938, 1940, 1942), Einarson, Neel, and Strömgren (1944), and others. However, the cases hitherto described

under that term have invariably shown a pattern of myelin involvement and a cytological picture so different from what we have seen in our own material that they are clearly unrelated. The very interesting case published by H. J. Scherer under the title "Glioblastomatose en plaques," in which the author postulated a neoplastic alteration in reacting cells in an instance of multiple sclerosis, represents in our opinion the coincident appearance of classical multiple sclerosis and of an infiltrating glioma in the same patient.

The question might be raised as to whether the lesions may represent scattered foci of encephalomalacia such as have been described in the spinal cord in leukæmia and chloroma by Critchley and Greenfield (1930). However, we did not find any evidence of vascular occlusion despite careful search in serial sections of typical lesions. Furthermore the appearance of the lesions themselves, and their apparent development from small foci to large ones, does not suggest an ischæmic origin.

There are in addition a few other conditions associated with multiple destructive lesions of cerebral white matter. These include subacute degeneration of the brain, as described by Adams and Kubik (1944) and others, carbon monoxide asphyxia (Meyer, 1928) and some cases of cerebral anoxia (Courville, 1953), and Hand-Schüller-Christian disease (Davison, 1933). However, in all of these the pattern and detailed structure of the lesions differ so greatly from those in our material that confusion between them does not seem likely.

These considerations, then, prompt us to look upon this disease process as an entity unique among demyelinative disorders. The question may now be raised as to whether a similar neuropathological disorder has been reported by other authors.

Review of the Literature

In 1930, among a group of cases with unusual neuropathological features not classifiable under any well-established disease entities, Hallervorden reported two cases which are strikingly similar to those we have described. His first case was that of a 45-year-old man, previously well, who developed a progressive illness characterized by dementia, impairment of vision, unsteadiness of gait, and, in the terminal stages, generalized rigidity, with a total duration of one year. Post-mortem examination showed miliary tuberculosis of the left lung and a tuberculous lesion of the left kidney. In the brain there were numerous white matter lesions most frequently occurring at the junction between cortex and white matter, often extending into the lower layers of cortex. These were small, round or oval, and tended to become confluent and to extend for considerable distances along the convolutions. These lesions occurred principally in the posterior parts of both cerebral hemispheres with a scattering of them in the basal ganglia; there were none of periventricular

XUM

distribution. Microscopically, they were characterized by myelin-sheath destruction with relative preservation of axis-cylinders. Not only were the lesions of the same form and character as seen in our cases, but in addition an outstanding feature was the presence of large numbers of gigantic astrocytes with single or multiple nuclei of bizarre appearance, closely resembling those encountered in our cases. No mitoses were seen in them, however. No mention is made of any cells corresponding to the densely basophilic round nuclei found in our material. His second case was that of a 71-year-old woman with an illness of six months characterized by progressive dementia, aphasic disturbances, and choreiform movements. The results of the general post-mortem examination were not reported. The neuropathological findings were in all essential respects identical with those in his first case.

Winkelman and Moore in 1941 in a study entitled "Lymphogranulomatosis (Hodgkin's disease) of the nervous system" reported the case of a 41-year-old woman with Hodgkin's disease which probably was present for at least eighteen months before death. During the course of the illness she received radiotherapy because of pain in the back and in the limbs. Shortly before her death she became stuporous and developed a left hemiparesis with bilateral pyramidal tract signs. Post-mortem examination showed invasion of the cranial dura mater by lymphogranulomatous cells. In the brain there were widely disseminated patchy demyelinative lesions involving the cerebral hemispheres, particularly anteriorly, and the basal ganglia, with minimal involvement of the brainstem and the cerebellum. A diagnosis of lymphogranulomatous invasion of the brain was made on the basis of the microscopic study. Through the great kindness of Dr. Matthew Moore, we have been privileged to examine sections from this case. The microscopical findings in the brain are the same as those in our 3 cases. The cells identified by Winkelman and Moore as Sternberg-Reed cells we believe to be giant astrocytes, identical to those seen in our material. In addition there were numerous examples of the densely basophilic round nuclei which we believe to be altered oligodendrocytes. We can only conclude that this case represents the same disease process met with in our cases, rather than direct lymphogranulomatous invasion of the brain.

In a case study entitled "Hodgkin's disease associated with Schilder's disease," Bateman, Squires, and Thannhauser, in 1945, described the case of a 43-year-old man with known Hodgkin's disease of two years' duration, who developed dementia, progressive visual loss, and dysarthria with death in three months. Two months after the onset of neurologic symptoms, a course of radiotherapy was given to the head, with no change in the course of the illness. A lumbar puncture showed no abnormalities. Post-mortem examination confirmed the diagnosis of Hodgkin's disease. There was, in addition, an extensive demyelinative process in the cerebral

XUM

white matter, most pronounced in the occipital lobes. Through the kind co-operation of Dr. S. J. Thannhauser, and Dr. H. E. MacMahon, Professor of Pathology, Tufts University School of Medicine, Boston, Massachusetts, we have been privileged to examine sections from this case. There are numerous small round or oval foci which merge together to form large confluent lesions. The cytological features are identical to those found in our cases. We therefore believe that this case does not represent Schilder's disease but instead is another example of the disease process now under discussion.

In 1955 Christensen and Fog reported a case considered to be Schilder's disease in an adult. The patient, a 59-year-old man, developed a progressive neurological disorder characterized by reading and writing difficulties, visual loss, impairment of memory, mental dullness, aphasia, and late in the illness, blindness, agitation, stupor and bilateral pyramidal tract signs. The total duration of this illness was six months. A lumbar puncture showed a normal cell-count and a slight elevation of protein. In addition the patient was considered to have sarcoidosis and was treated with ACTH. Post-mortem examination showed sarcoidosis of the lungs, spleen, kidneys and lymph nodes. In the brain there was extensive disease of the white matter of the posterior parts of the cerebral hemispheres and the corpus callosum. Microscopical examination showed complete loss of myelin in the involved areas, with disappearance of axis cylinders, and an intense cellular reaction. A noteworthy feature was the presence of numerous monstrous astrocytes. Through the generosity of Dr. Erna Christensen we have been privileged to examine sections from this case. These show large numbers of small perivascular demyelinative foci which tend to become confluent. Within the large lesions there are numerous giant astrocytes which appear identical to those seen in our material; there are no mitoses in them, however. At the periphery of the lesions there are many examples of the densely basophilic round nuclei, some of which contain intranuclear inclusions that resemble those seen in our cases. We therefore believe that this case likewise is an instance of the unusual demyelinative disease encountered in our material.

These previously reported cases as well as our own observations are summarized in Table I. It is immediately clear that the neuropathological changes, which were the same in all, were associated, in a large proportion of the group, with previously existing neoplastic disorders of lymphatic tissue (Hodgkin's disease in 3 cases, chronic lymphatic leukæmia in 2). Sarcoidosis was found in 1 case, tuberculosis in 1, whereas in 1 no associated generalized disease state was mentioned. We may therefore safely conclude that the unique demyelinative disorder we have described may occur as a complication, hitherto unrecognized, of Hodgkin's disease and chronic lymphatic leukæmia. The question may now be raised as to whether the clinical features of this condition are sufficiently characteristic to permit future recognition of such cases.

XUM

Clinical Features

Although the small number of cases does not permit a complete delineation of the clinical picture, review of the case histories allows some general statements to be made. The onset of the neurological symptoms bears no apparent relationship either to the severity or duration of the underlying disease process; such symptoms have appeared as early as eight months or as late as fifteen years after the original diagnosis had been made. Once established, the neurological disease pursues a relentlessly progressive course, with death in most instances in two to six months. Despite some variation from case to case, certain clinical manifestations predominate—for instance, dementia, alteration in the state of consciousness, language disorders, visual impairment, and evidence of pyramidal-tract involvement. Less common were cranial nerve palsies and sensory deficits. Headache occurred in only one case (present Case 2). Seizures did not occur in any of the cases. Choreiform movements were described in one.

The cerebrospinal fluid was remarkable for the absence of significant abnormalities despite the presence of extensive destruction of brain parenchyma. The electroencephalogram done in 3 cases was abnormal in all without specific or characteristic patterns.

In summary, then, the signs and symptoms are those of a subacute progressive cerebral disorder involving most severely the posterior parts of the cerebral hemispheres without evidence of increased intracranial pressure or significant abnormalities in the cerebrospinal fluid.

Incidence

In order to ascertain the approximate frequency of this neurological condition as a complication of leukæmia or malignant lymphoma, the records of post-mortem examinations at the Massachusetts General Hospital over a twenty-year period (between January 1, 1937, and December 31, 1956) were reviewed. During this period of time 10,984 autopsies were performed. In this group, there were 234 established cases of leukæmia or malignant lymphoma in which the nervous system was examined. Of those cases, only 2 (Cases 1 and 2 of the report) showed the neuropathological process under discussion. In view of the possibility that the condition may have existed in cases in which the nervous system was not examined, an exact statement as to incidence cannot be given. Nevertheless the extreme rarity of this condition is immediately apparent.

Ætiological Considerations

We do not know the cause of this condition. It is impressive that 5 out of the 8 cases were associated with a neoplastic disorder of lymphatic tissue, but the fact remains that in at least 2 others this association clearly was not present. Thus, although the condition has been most frequently

XUM

met with as a complication of chronic lymphatic leukæmia or Hodgkin's disease, these disorders are not absolutely required for its development. Whether there is some factor shared in common between these diseases and sarcoidosis and tuberculosis that may be responsible for the neurological lesions remains entirely unknown.

It might then be asked whether any form of treatment the patients received could have resulted in brain lesions of the type described. It is quite evident, however, that no one form of treatment was used in all the cases. That most frequently employed was radiation therapy. This was not given in large amounts to the head region in any case before the onset of neurological symptoms, and was not given at all in 3 out of the 8. In addition, the lesions do not resemble in any way those known to be the result of excessive radiation (cf. Hicks, 1953). Other forms of treatment used included ACTH (2 cases), nitrogen mustard (1 case), triethylene-melamine (2 cases), and radioactive gold into the pleural space (1 case). Obviously such treatment measures which were only occasionally used cannot be held responsible.

The cerebral lesions cannot be ascribed to disease of the blood vessel walls or vascular occlusions, for these abnormalities did not occur in any of the cases.

Summary

(1) 3 cases are presented of an unusual demyelinative disease process developing in adult life on a background of chronic lymphatic leukæmia (2 cases) and Hodgkin's disease (1 case). The lesions are characterized by widely disseminated small perivascular foci of destruction of myelin-sheaths with relative sparing of axis-cylinders. These foci have shown a pronounced tendency to become confluent so that large plaque-like lesions may occur. Most severely affected were the posterior parts of the cerebral hemispheres, although all levels of the brain could be involved. Associated with the myelin destruction was a distinctive cytological reaction consisting of hypertrophy of astrocytes into bizarre gigantic forms, with unequivocal mitoses in Case 1 suggesting neoplastic cells in appearance, and alteration of oligodendrocytes with the production of hitherto undescribed large round densely basophilic nuclei.

(2) Review of the literature discloses 5 additional cases of the same neuropathological process occurring in a background of Hodgkin's disease in 2 cases, sarcoidosis in 1 case and tuberculosis in 1 case. In 1 case the underlying disease process, if any, is unknown.

(3) The clinical features of these cases are reviewed.

(4) It is suggested that the neurological disease occurs as a complication of Hodgkin's disease or chronic lymphatic leukæmia, although its occurrence with other disease states implies that these diseases are not absolutely required for its production.

XUM

(5) The neurological disease cannot be related in any way to various forms of treatment used for Hodgkin's disease or chronic lymphatic leukæmia.

(6) Evidence is adduced that we are dealing with a hitherto unrecognized neuropathological entity. The cause remains undisclosed.

ACKNOWLEDGMENTS

We should like to acknowledge our gratitude to Dr. Raymond D. Adams, Bullard Professor of Neuropathology, Harvard Medical School, and Chief of Neurology Service, Massachusetts General Hospital, Dr. Benjamin Castleman, Clinical Professor of Pathology, Harvard Medical School, and head of Pathology Department, Massachusetts General Hospital, Dr. Charles Kubik, Consultant in Neuropathology, Massachusetts General Hospital, and Professor J. Hallervorden, Chief of the Neuropathologic Division, Max-Planck-Institut für Hirnforschung, Giessen, Germany (Director: Professor H. Spatz), for helpful advice.

REFERENCES

ADAMS, R. D., and KUBIK, C. S. (1944) *New Engl. J. Med.*, **231,** 1.
——, —— (1952) *Amer. J. Med.*, **12,** 510.
BATEMAN, O. J., Jr., SQUIRES, G., and THANNHAUSER, S. J. (1945) *Ann. intern. Med.*, **22,** 426.
VAN BOGAERT, L. (1945) *J. Neurol. Neurosurg. Psychiat.*, **8,** 101.
CHRISTENSEN, E., and FOG, M. (1955) *Acta Psychiat., Kbh.*, **30,** 141.
COURVILLE, C. (1953) "Cerebral Anoxia." Los Angeles.
CREUTZFELDT, H. G. (1923) *Arch. Psychiat. Nervenkr.*, **68,** 485.
CRITCHLEY, M., and GREENFIELD, J. G. (1930) *Brain*, **53,** 11.
DAVISON, C. (1933) *Arch. Neurol. Psychiat., Chicago*, **30,** 75.
DAWSON, J. R., Jr. (1933) *Amer. J. Path.*, **9,** 7.
—— (1934) *Arch. Neurol. Psychiat., Chicago*, **31,** 685.
DIAMOND, I. B. (1934) *Arch. Neurol. Psychiat., Chicago*, **32,** 118.
EINARSON, L., and NEEL, A. V. (1938) *Acta Jutland.*, **10,** 2.
——, —— (1940) *Acta Jutland.*, **12,** 3.
——, —— (1942) *Acta Jutland.*, **14,** 2.
——, —— and STRÖMGREN, E. (1944) *Acta Jutland.*, **16,** 1.
EUGÉNIS, C. (1929) "Les manifestations cérébro-médullaires de l'adénie eosinophilique prurigène." Thése de Lyon.
FERRARO, A., and MORRISON, L. R. (1928) *Psychiat. Quart.*, **2,** 506.
FRIED, B. M. (1926) *Arch. Path.*, **2,** 23.
GINSBURG, S. (1927) *Arch. Intern. Med.*, **39,** 571.
GOLDMAN, L. B. (1940) *J. Amer. med. Ass.*, **114,** 1611.
VON HAGEN, K. O. (1937) *Bull. Los Angeles neurol. Soc.*, **2,** 20.
HALLERVORDEN, J. (1930) "Eigenartige und nicht rubrizierbare Prozesse." *In* Bumke's "Handbuch der Geisteskrankheiten," Berlin. **11,** 1063.
VON HECKER, H., and FISCHER, W. (1922) *Dtsch. med. Wchschr.*, **48,** 482.
HICKS, S. P. (1953) *Res. Publ. Ass. nerv. ment. Dis.*, **32,** 439.
JACKSON, H., Jr., and PARKER, F., Jr. (1944) *New Engl. J. Med.*, **230,** 1.
—— (1945) *New Engl. J. Med.*, **233,** 369.
LEIDLER, F., and RUSSELL, W. O. (1945) *Arch. Path.*, **40,** 14.

XUM

PLATE VII

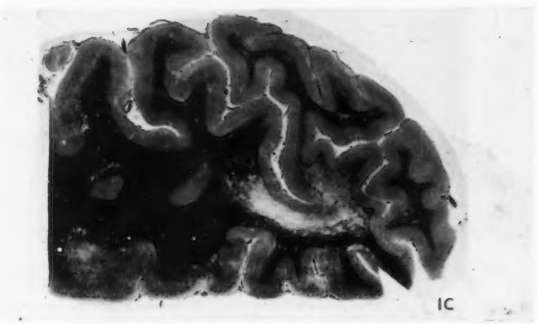


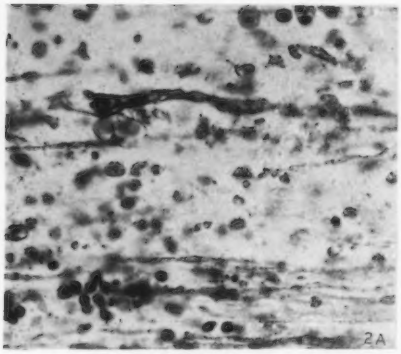
FIG. 1A (*Case* 1).—Horizontal section of posterior two-thirds of right hemisphere showing two large lesions. Note the confluence of minute foci in the anterior lesion (left in photograph) and the sharply demarcated posterior borders, with the less well defined anterior border, of the posterior lesion which involves the U-fibres and deeper layers of the cortex in several places. Loyez myelin stain. ×1.

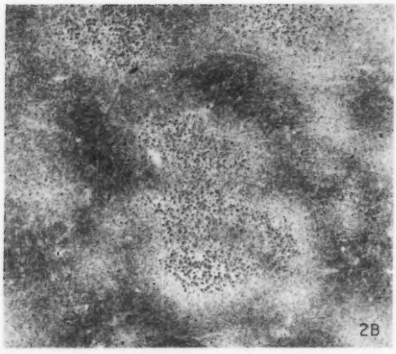
FIG. 1B (*Case* 1).—Horizontal section through right frontal lobe, showing confluence of numerous demyelinative foci in the convolutional white matter, and one discrete intracortical lesion. Loyez myelin stain. ×2.

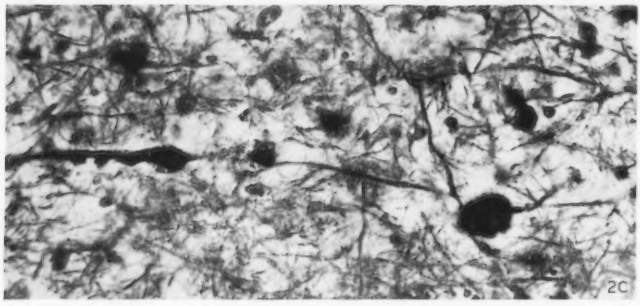
FIG. 1C (*Case* 1).—Horizontal section through left occipito-parietal region showing confluence of numerous small foci. Loyez myelin stain. ×1.

To illustrate article by Karl-Erik Åström, Elliott L. Mancall and Edward P. Richardson, Jr.

XUM







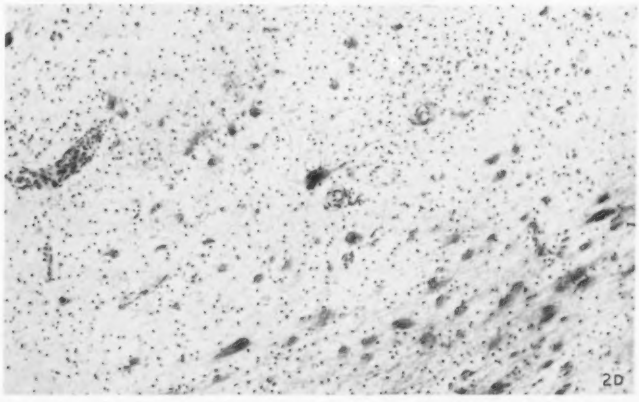


FIG. 2A (*Case* 1).—Swelling and fragmentation of myelin sheaths within the peripheral zone of the large lesion. Loyez myelin stain. ×450.

FIG. 2B (*Case* 1).—Lesions containing fat-filled macrophages. These cells are absent in the small lesions. Oil red O stain for fat. ×37.

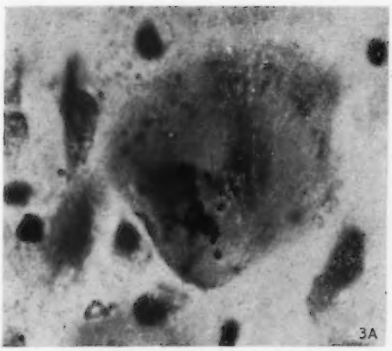
FIG. 2C (*Case* 1).—Totally demyelinated lesion showing relative preservation of axis cylinders. Several extremely abnormal axons are shown. Cajal silver method. ×450.

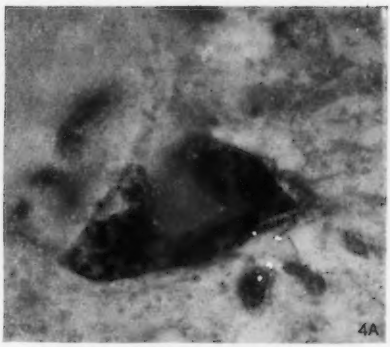
FIG. 2D (*Case* 1).—Central portion of large lesion showing many large fibrous astrocytes and macrophages (small dark nuclei). Note the giant astrocyte with hyperchromatic irregular nucleus and stellate processes, one of which can be followed to a near-by blood vessel. Hæmatoxylin and eosin. ×125.

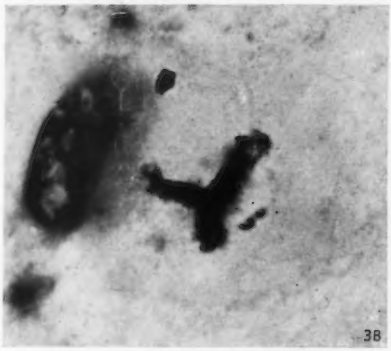
To illustrate article by Karl-Erik Åström, Elliott L. Mancall and Edward P. Richardson, Jr.

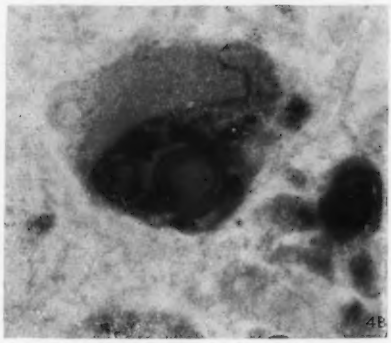
XUM

PLATE IX









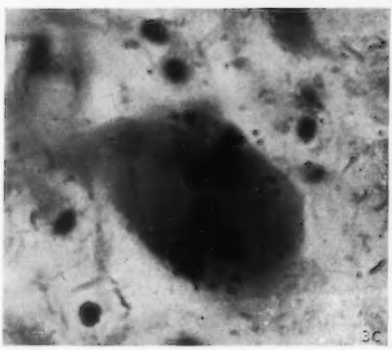


FIG. 3A (*Case* 1).—Multipolar mitosis in a giant astrocyte. Cresyl violet. ×1,000.

FIG. 3B (*Case* 1).—Tripolar mitosis in a giant astrocyte. Cresyl violet. ×1,000.

FIG. 3C (*Case* 1).—Giant astrocyte containing two mitoses. Hæmatoxylin and eosin. ×1,000.

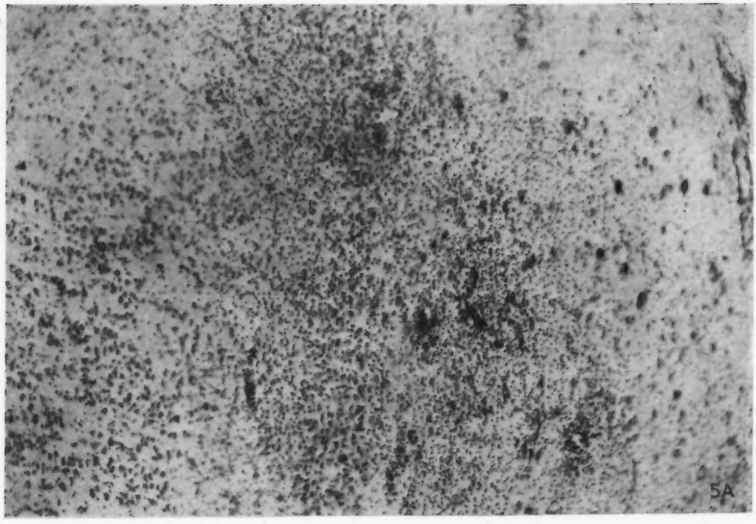
FIG. 4A (*Case* 2).—Giant multinucleated astrocyte. Hæmatoxylin and eosin. ×1,000.

FIG. 4B (*Case* 2).—Giant astrocyte with homogeneous vesicular inclusions. Hæmatoxylin and eosin. ×1,000.

FIG. 4C (*Case* 3).—Giant astrocyte with hyperchromatic nucleus. Hæmatoxylin and eosin. ×1,000.

To illustrate article by Karl-Erik Åström, Elliott L. Mancall and Edward P. Richardson, Jr.

XUM



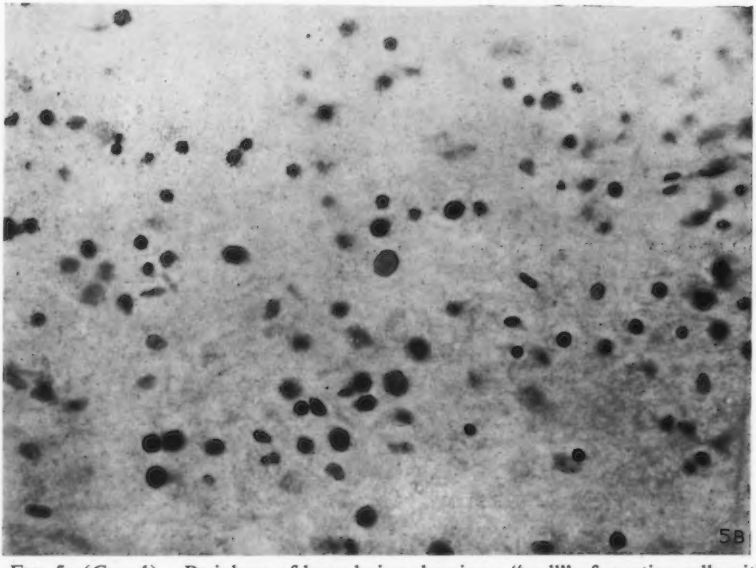


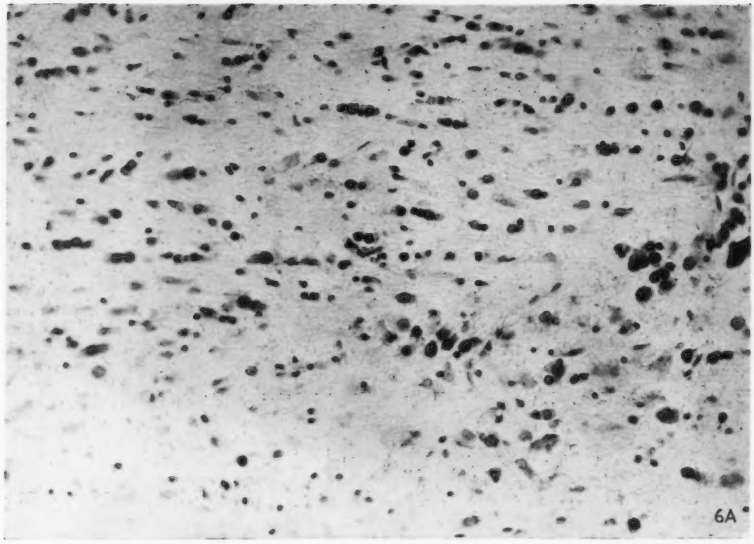
FIG. 5A (*Case* 1).—Periphery of large lesion showing a "wall" of reacting cells with normal cortex on the left and the more central portion of the lesion on the right. Hæmatoxylin and eosin. ×125.

FIG. 5B (*Case* 1).—Periphery of a lesion showing several densely basophilic round nuclei larger than those of normal oligodendrocytes, which also appear in the photograph. One nucleus in the centre contains an intranuclear inclusion with marginal arrangement of chromatin. Cresyl violet. ×450.

To illustrate article by Karl-Erik Åström, Elliott L. Mancall and Edward P. Richardson, Jr.

XUM

PLATE XI



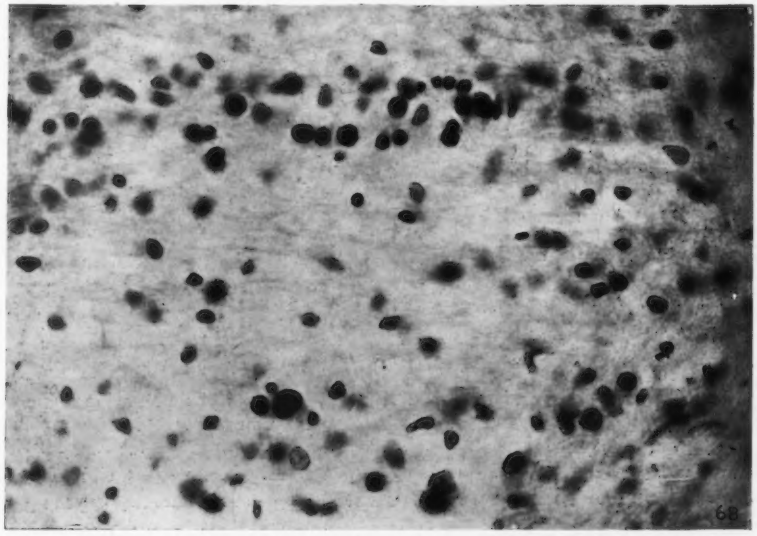


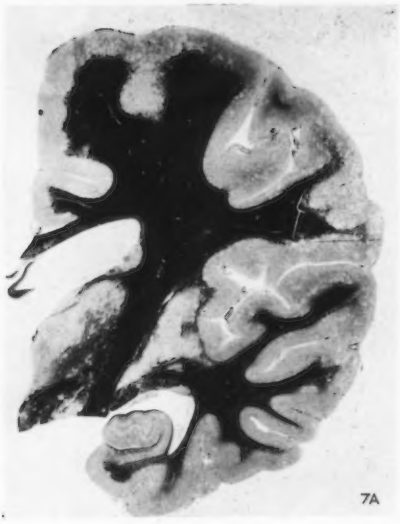
FIG. 6A (*Case* 2).—Border of lesion in internal capsule showing presence of abnormal densely basophilic round nuclei in interfascicular rows together with normal oligodendrocytes. The lesion is in the lowermost part of the photograph. Cresyl violet. ×250.

FIG. 6B (*Case* 1).—Border of lesion in optic radiation, showing rows of densely basophilic round nuclei. Hæmatoxylin and eosin. ×450.

To illustrate article by Karl-Erik Åström, Elliott L. Mancall and Edward P. Richardson, Jr.

XUM

PLATE XII



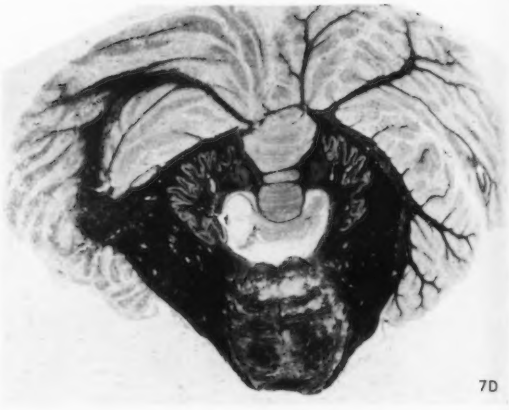


FIG. 7A (*Case* 2).—Coronal section of left cerebral hemisphere showing numerous small demyelinated foci. Loyez myelin stain. ×1.

FIG. 7B (*Case* 2).—Coronal section of left hemisphere posteriorly showing a large demyelinative lesion and numerous small foci. The superficial lesion involving cortex on the right in the photograph represents a surgical puncture wound. Loyez myelin stain. ×1·5.

FIG. 7C (*Case* 2).—Horizontal section of mid-brain showing numerous lesions. Loyez myelin stain. ×2.

FIG. 7D (*Case* 2).—Horizontal section of pons and cerebellum showing numerous lesions of varying size. Loyez myelin stain. ×1·5.

To illustrate article by Karl-Erik Åström, Elliott L. Mancall and Edward P. Richardson, Jr.

XUM

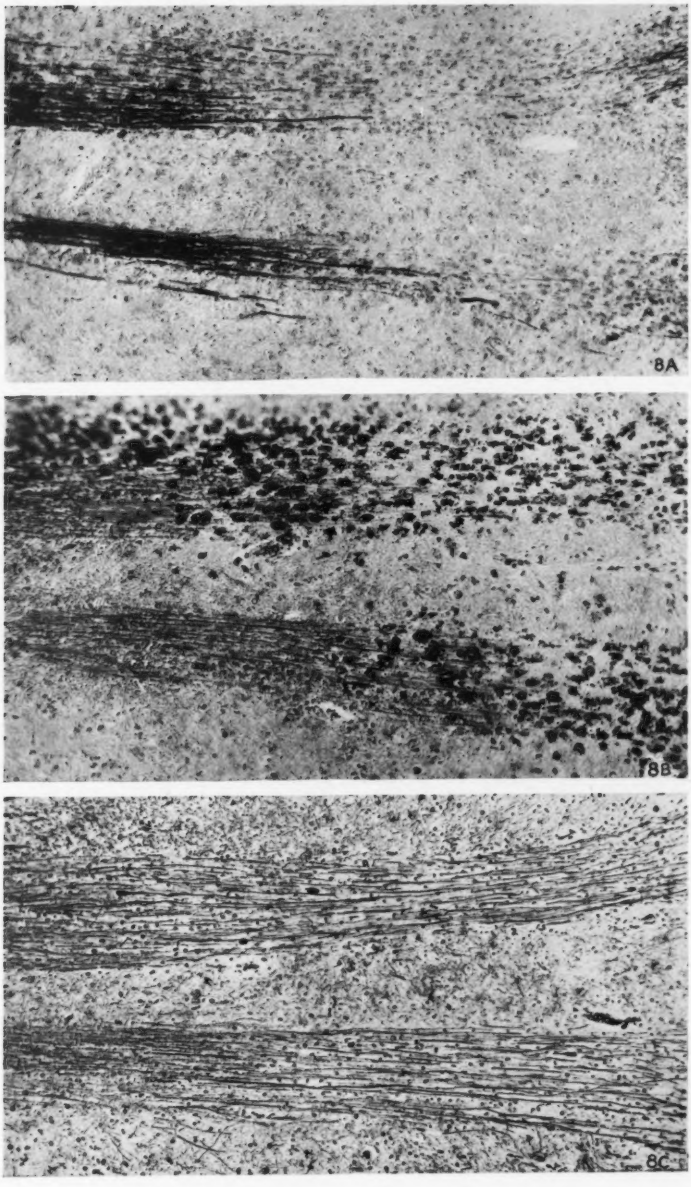
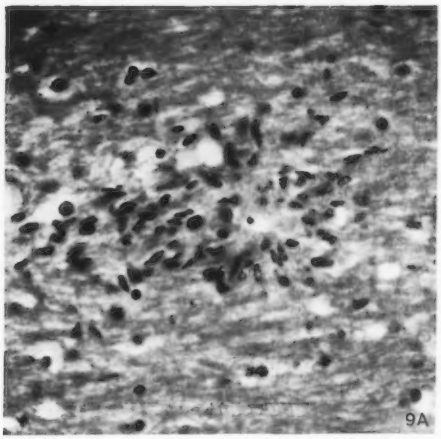
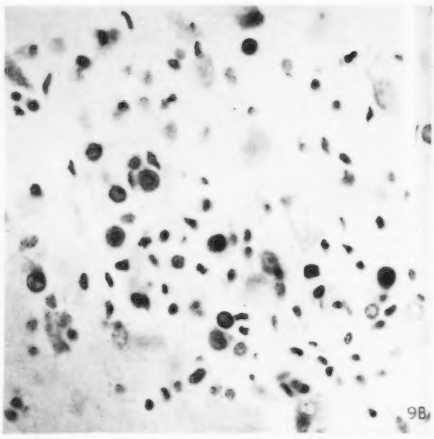
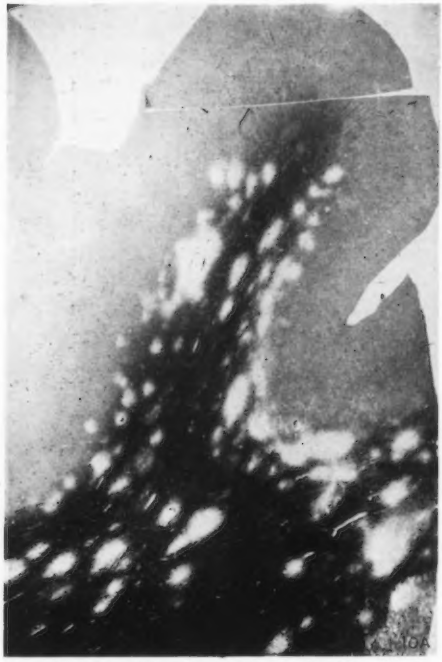


FIG. 8 (*Case* 2).—Adjacent sections of small lesions in putamen showing in A, loss of myelin sheaths; in B, presence of sudanophilic material in macrophages; and in C, relative preservation of axis cylinders. A, Loyez myelin stain. ×450. B, Oil red O stain for fat. ×450. C, Cajal silver method. ×450.

To illustrate article by Karl-Erik Åström, Elliott L. Mancall and Edward P. Richardson, Jr.







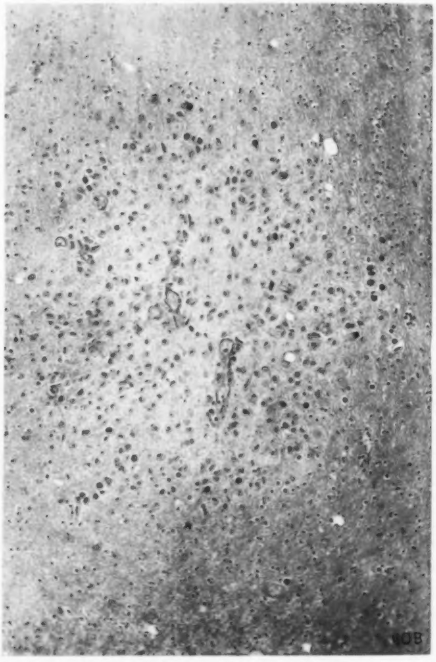


FIG. 9A (*Case* 2).—Tiny collection of microglia representing smallest discernible lesion. Hæmatoxylin and eosin. ×450.

FIG. 9B (*Case* 2).—Slightly larger lesion than that in A. Several of the typical darkly basophilic nuclei are shown, some of which contain intranuclear inclusions. Cresyl violet. ×450.

FIG. 10A (*Case* 3).—Sprinkling of small lesions with some tendency to confluence. Heidenhain-Woelcke myelin stain. ×11·5.

FIG. 10B (*Case* 3).—Typical lesion showing centrally located venules, macrophages, and peripherally arranged densely basophilic nuclei. Hæmatoxylin and eosin. ×125.

To illustrate article by Karl-Erik Åström, Elliott L. Mancall and Edward P. Richardson, Jr.

XUM

MEYER, A. (1928) *Z. ges. Neurol. Psychiat.*, **112,** 172.
NONNE, M. (1897) *Dtsch. Z. Nervenheilk.*, **10,** 165.
PETERS, G. (1935) *Z. ges. Neurol. Psychiat.*, **153,** 356.
ROTTINO, A., and HOFFMAN, G. (1950) *J. Neuropath.*, **9,** 103.
SCHERER, H. J. (1938) *J. belge Neurol.*, **38,** 1.
SCHRICKER, J. L. Jr., and SMITH, D. E. (1955) *Cancer, Philad.*, **8,** 629.
SCHWAB, R. S., and WEISS, S. (1935) *Amer. J. med. Sc.*, **189,** 766.
SHAPIRO, P. F. (1930) *Arch. Neurol. Psychiat., Chicago*, **24,** 509.
SPARLING, H. J., Jr., and ADAMS, R. D. (1946) *Arch. Path.*, **42,** 338.
——, ——, and PARKER, F., Jr. (1947) *Medicine, Baltimore*, **26,** 285.
VIETS, H. R., and HUNTER, F. T. (1933) *Arch. Neurol. Psychiat., Chicago*, **29,** 1246.
WEIL, A. (1931) *Arch. Neurol. Psychiat., Chicago*, **26,** 1009.
WINKELMAN, N. W., and MOORE, M. T. (1941) *Arch. Neurol. Psychiat., Chicago*, **45,** 304.

XUM

AN EVALUATION OF THYMECTOMY IN MYASTHENIA GRAVIS

BY

JOHN A. SIMPSON[1]

(From The Neurological Research Unit of the Medical Research Council, The National Hospital, Queen Square, London)

FEW diseases have been more satisfying to the teacher of medicine than myasthenia gravis for no better meeting ground exists for clinician, physiologist and pharmacologist. Ten years ago the standard teaching was that the myasthenic response must indicate one of three possible "chemical lesions" at the neuromuscular junction: (i) insufficiency of acetylcholine, (ii) excess of cholinesterase, or (iii) a "curariform" block of transmission, presumably due to a substance carried in the blood. More recently the logical fourth possibility of an abnormality of the motor end-plates of muscle has been postulated. It seemed only a matter of time and of refinement of physiological and pharmacological techniques before the true lesion would be demonstrated. In that same period knowledge of the physiology of the neuromuscular junction has made its greatest advances, yet the solution of the problem of myasthenia evades us despite renewed and world-wide interest as evinced by two recent symposia (*Acta neurol. psychiat. belg.*, 1955; *Amer. J. Med.*, 1955).

Fundamental to any satisfactory theory is an explanation of the role of the thymus gland. It is not the purpose of this paper to reconsider the evidence that the thymus gland is implicated in myasthenia gravis; this has been admirably reviewed by McEachern (1943) and by Eaton, Clagett and Bastron (1953). The association of thymic pathology with myasthenia gravis has been recognized for more than fifty years and is not in question, but mere association is less important than the concept that it may be causally related to the transmission defect in muscle. It is difficult to implicate the thymus in any "chemical pathology" of myasthenia gravis with the possible exception of the neuromuscular block theory, and it is significant that the exponents of the other theories make no serious efforts to solve the dilemma. The evidence for causal relationship is of two types, (*a*) thymic extracts may have neuromuscular blocking properties, and (*b*) operative removal or radiotherapeutic destruction of the gland is followed

[1]Present address: Neurological Division, Department of Medicine, Edinburgh University.

by significant improvement in patients suffering from myasthenia gravis. Evidence of the first type and its antithesis has been reviewed recently by Wilson and Wilson (1955); the present paper is designed to review the evidence of the second type and to present the results of an independent survey of the largest series yet reported. A preliminary account has been presented (Simpson, 1956).

Material and Methods

The records of all patients diagnosed as myasthenia gravis at the National Hospital for Nervous Diseases since 1934 were scrutinized and an attempt made to trace survivors and to determine the fate of those who had died. Most of the cases seen after 1941 were subjected to thymectomy, the majority by Sir Geoffrey Keynes. The survey was extended by kind invitation of Sir Geoffrey to include his full series operated on at Saint Bartholomew's and New End Hospitals.

Criteria for inclusion of cases in the survey were:

(*a*) A firm diagnosis of myasthenia gravis by a consultant neurologist to one of these hospitals.

(*b*) A convincing case history of loss of muscle power after exercise, relieved by rest.

(*c*) Documented evidence of improvement with neostigmine (even if only a test injection).

(*d*) Absence of evidence of central neurological disease.

A total of 404 cases was available for study. Where death was not known to have occurred the patients were invited to attend the National Hospital for examination. All were traced except 12 operated and 18 not-operated patients. Doctors and hospital records were consulted for evidence of the cause of death in non-survivors. Where this was impossible the certified cause of death was ascertained. Of the 245 known survivors who could be traced, 181 were examined personally and 64 patients who were unable to attend the hospital (mainly due to residence abroad) were asked to complete a detailed questionnaire with the assistance of their family doctor.

The operated cases were classified in the following categories in which the essential feature is a comparison of the state at the time of follow-up with the state before operation with respect to (i) presence of signs and symptoms of myasthenia, (ii) exercise tolerance, (iii) drug requirements.

Category A: Full working life with no restriction. No neostigmine required. No subjective weakness. A small degree of permanent objective weakness, unrelieved by neostigmine, is permitted. The present state must represent a marked improvement from the original.

XUM

Category B: Able to lead a full life with only minor myasthenic symptoms, requiring no neostigmine or controlled by not more than 4 tablets (60 mg.) daily. A significant improvement is required.

Category C: Full life with few restrictions but (*a*) demonstrable myasthenia not requiring neostigmine, or (*b*) still requiring neostigmine but at least 40 per cent less than before and with improved response.

Category D: (*a*) Improved, but neostigmine requirements unchanged or increased, (*b*) unimproved, irrespective of neostigmine dosage, (*c*) worse.

Post-operative death.—Death occurring within three weeks of operation.

Myasthenic death.—Death occurring at a later date where the history suggested asphyxial death or death not explicable by other causes.

Death from other causes.—Death directly attributable to significant disease where the history suggested that myasthenia was not a major factor (e.g. cerebral hæmorrhage).

Patients who had not been treated by thymectomy were assessed by the same criteria with reference to the condition on first admission to hospital. The essential feature is an assessment of *change of status*, hence a patient with little disability (e.g. ocular myasthenia) does not qualify for a high category if this state is not significantly better than at the datum point. In case of doubt a patient was assigned to the lower category.

The data were analysed statistically with respect to sex, age at onset, duration of symptoms before the datum point, and length of follow-up to determine whether the two series ("operated" and "not-operated") could be accepted as representative samples of the population of myasthenics. Cases known to have a thymoma were considered separately. These analyses will be presented before comparing the natural history of the two series.

PART I

Comparison of "Operated" and "Not-operated" Series

The *sex distribution* and the *frequency of thymic tumours* in the two series is shown in Table I. It is, of course, possible that some thymic tumours

TABLE I.—DISTRIBUTION OF THYMIC TUMOURS

	Operated			*Not-operated*			
Sex	*Non-tumour*	*Thymoma*	%	*Non-tumour*	*Thymoma*	%	*All cases*
Female ..	182	23	11·4	59	6	9·2	270
Male ..	76	13	14·6	40	5	11·1	134
Both ..	258	36	12·3	99	11	10·0	404

have not been diagnosed in the not-operated patients, but the close resemblance of the two series suggests that this is not so. Table I does, however, show a difference in the sex distribution. This is further analysed for non-tumour cases in Tables II and III and in fig. 1.

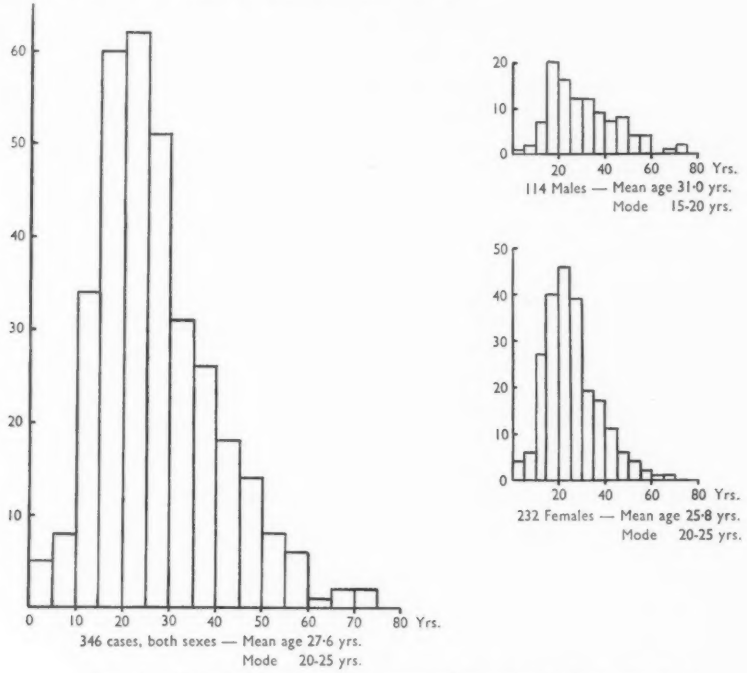


FIG. 1.—Distribution of age at onset of myasthenia (non-tumour).

TABLE II.—SEX DISTRIBUTION (NON-TUMOUR CASES)

	Operated			*Not-operated*		
Age at onset	*F*	*M*	*Ratio*	*F*	*M*	*Ratio*
Years						
0–10	9	2	4·5 : 1	1	1	1 : 1
11–20	62	20	3·1 : 1	8	8	1 : 1
21–30	67	24	2·8 : 1	21	8	2·6 : 1
31–40	23	17	1·4 : 1	16	6	2·7 : 1
41–50	11	10	1·1 : 1	6	6	1 : 1
51–60	2	1	(2 : 1)	4	8	1 : 2
61–70				2	1	2 : 1
71–80					2	
Unknown	8	2		1		
Total	182	76	2·4 : 1	59	40	1·5 : 1
Mean (years)	23·7	27·9		32·3	36·9	

XUM

Table II and fig. 1 showing the *age at onset*, reveal marked differences between the two series. Inspection of the histograms of fig. 1 suggests that there is an incidence of age-at-onset which has a skew distribution about a modal value of 20 years (approx.) and that this does not differ greatly with sex, although the males have relatively more cases in the older age groups (causing a higher average age). This difference could be due to the small numbers of males, and might disappear in a larger series, but the same trend was reported by Grob and Harvey (1953). The regularity of the distribution curves in the operated series alone and in the total series suggests that they must closely represent the true population of myasthenic subjects if the age of onset is not randomly distributed. There is a preponderance of females of 4·5–1 in the first decade which steadily decreases to unity in the fifth decade (numbers are too small to attribute any significance to the possible reversal of sex incidence in later age groups). On this interpretation the "not-operated" series is gravely deficient in females under the age of 20 and contains relatively more males over 50 (hence the higher mean age for both sexes) (Table II). The series are closely similar for the age period from 16 to 35 which contains two-thirds of the operated series, though only half of the not-operated series (Table III). It will be necessary to make all comparisons in this section of the case

TABLE III.—THE AGE-GROUP 16–35

Age at onset Years	*Operated*		*Not-operated*	
	F	*M*	*F*	*M*
16–20	36	15	6	6
21–25	37	13	12	5
26–30	30	10	9	3
31–35	13	11	8	2
Total	116	49	35	16
Ratio	2·3	1	2·2	1

material before accepting conclusions derived from comparison of the whole of both series, since the value of thymectomy has been stated to be most evident in women who develop myasthenia at an early age.

The *length of survival* from the onset of myasthenic symptoms (to April 1956) is shown in Table XV. It will be more convenient to discuss the breakdown into categories later. The mean survival is closely similar in the two series, indeed despite the longer time at risk in the not-operated series it is slightly lower than in the operated series, due to the long-duration survivors being matched by a higher proportion of deaths within a few years of the onset.

Associated phenomena of myasthenia gravis occurred with equal frequency in both series (non-tumour) (Table IV). "Myopathy" represents

TABLE IV.—ASSOCIATED PHENOMENA (NON-TUMOUR SERIES)

	Operated		*Not-operated*	
	F	*M*	*F*	*M*
	%	%	%	%
Ocular Myasthenia	1·6	5·3	1·2	20·0
Myopathy	9·3	22·4	10·2	15·0
Goitre ..	18·0	9·0	8·5	2·5

permanently weak wasted muscles not improved by neostigmine. "Goitre" includes simple non-toxic enlargement of the thyroid and thyrotoxicosis. "Ocular myasthenia" indicates the proportion of cases in which the myasthenia remained confined to the extra-ocular muscles (including orbicularis oculi) for the duration of the survey.

PART II

Results

The classification of both series in April 1956 is shown in Table V and in percentage form in fig. 2. There are three questions to be answered by this survey: (i) Is there any significant difference in prognosis between the two groups? (ii) If there is any benefit to be gained from thymectomy, is it obtained by both sexes? (iii) Are there any other factors which affect the response to operation?

TABLE V.—RESULTS—NON-TUMOUR

	Operated				*Not-operated*			
	F		*M*		*F*		*M*	
Category	*No.*	%	*No.*	%	*No.*	%	*No.*	%
A	40	22·0	15	19·7	9	15·3	7	17·5
B	24	13·2	8	10·5	3	5·1	2	5·0
C	42	23·1	18	23·7	9	15·3	3	7·5
D	32	17·6	15	19·7	8	13·5	10	25·0
Data incomplete	13	7·1	4	5·3	9	15·3	9	22·5
Myasth. deaths	14	7·7	9	11·8	17	28·8	8	20·0
Post.-op. deaths	14	7·7 } 17·0	6	7·9 } 21·0	—	} 35·6	—	} 22·5
Deaths, other	3	1·6	1	1·3	4	6·8	1	2·5
Total	182		76		59		40	

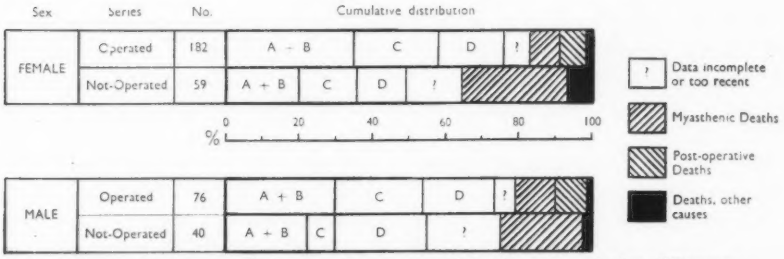


FIG. 2.—Comparison of series (non-tumour) to show cumulative difference.

TABLE VI.—COMPARISON OF TREATMENTS FOR EACH SEX

	Female		*Male*	
Category	*Difference**	*S.E. of diff.*	*Difference**	*S.E. of diff.*
A+B	+14·8†	6·3	+ 7·7	8·4
C	+ 6·8	5·6	+16·2†	6·4
D	+ 4·1	5·3	− 5·3	8·2
Myasth. deaths	−21·1†	6·2	− 8·2	7·3
All deaths	−18·6†	6·8	− 1·5	8·1

*Per cent in operated series minus per cent in not-operated series.
†Unlikely to occur by chance.

TABLE VII.—SEX-DIFFERENCE IN EACH SERIES

	Operated		*Not-operated*	
Category	*Difference**	*S.E. of diff.*	*Difference**	*S.E. of diff.*
A+B	+5·0	6·3	− 2·1	8·4
C	−0·6	5·8	+ 7·8	6·2
D	−2·1	5·4	−11·5	8·1
Myasth. deaths	−4·1	8·2	+ 8·8	8·6
All deaths	−4·0	5·4	+13·1	9·0

*Per cent females minus per cent males in each series. There is no significant difference.

The first two questions may be investigated concurrently.

Comparison of results. Sex differences.—For further statistical analysis, Categories A and B will be considered together as the distinction between them is a fine one of doubtful validity. All cases in these categories are for practical purposes without any disability due to myasthenia.

In Table VI the percentages in each category are compared separately for each sex. The difference is expressed as +ve if the proportion is greater in the operated series than in the not-operated, and −ve if otherwise. If a difference in percentage exceeds twice the standard error of the difference the odds are more than 20 : 1 against the difference being due to chance; such a difference is accepted as statistically significant. In Table VII a similar comparison is made between male and female in each series.

This analysis answers the first two questions. The operated series contains a higher proportion of females in Category A and B than would be likely to occur by chance (at the 5 per cent level), and the death-rate from myasthenia is very significantly reduced (Table VI). Even when the operative hazard is added, the total mortality rate is significantly lower than in the not-operated series. Males show a similar trend though the difference is not statistically significant except in Category C. Table VII suggests a possible explanation. Neither series shows a significant difference between the sexes. In the not-operated series there is a higher female mortality and fewer women than men reach Categories A and B, in the operated series this trend is completely reversed. It may be that thymectomy reverses an unfavourable prognosis for women, but any

conclusions must be tentative as the analysis does not exclude the possibility of the sex difference in either series having occurred by chance. As the benefit in favour of operation for women is unlikely to be due to chance it is possible that a larger series would show that the similar trend for males is equally significant. It is also possible that differences in composition of the series may be important. The following tables are of the same type as Tables V–VII for the age group 16–35.

TABLE VIII.—RESULTS IN AGE-GROUP 16–35

	Operated				*Not-operated*			
	F		*M*		*F*		*M*	
Category	*No.*	—	*No.*	%	*No.*	%	*No.*	%
A	24	20·7	11	22·5	6	17·1	2	12·5
B	17	14·6	7	14·3	1	2·9	1	6·3
C	31	26·7	12	24·5	4	11·4	1	6·3
D	21	18·1	8	16·3	6	17·1	4	25·0
Data incomplete	4	3·4	1	2·0	7	20·0	5	31·2
Myasth. deaths	9	7·7	7	14·3	10	28·6	2	12·5
Post-op. deaths	8	6·9	2	4·1	—	—	—	—
Deaths, other	2	1·7	1	2·0	1	2·9	1	6·3
Total	116		49		35		16	

TABLE IX.—COMPARISON OF TREATMENTS FOR EACH SEX (AGE 16–35)

	Female		*Male*	
Category	*Difference**	*S.E. of diff.*	*Difference**	*S.E. of diff.*
A+B	+15·3	16·8	+18·0	25·2
C	+15·3	17·7	+18·2	27·2
D	+ 1·0	17·5	− 8·7	21·9
Myasth. deaths	−20·9	16·8	+ 1·8	26·8
All deaths	−15·2	16·3	+ 1·6	25·9

*Per cent in operated series minus per cent in not-operated series. There is no significant difference.

TABLE X.—SEX-DIFFERENCE IN EACH SERIES (AGE 16–35)

	Operated		*Not-operated*	
Category	*Difference**	*S.E. of diff.*	*Difference**	*S.E. of diff.*
A+B	−1·5	13·6	+ 1·2	27·1
C	+2·2	14·7	+ 5·1	29·0
D	+1·8	15·5	− 7·9	23·4
Myasth. deaths	−6·6	15·9	+16·1	27·4
All deaths	−4·1	15·3	+12·7	26·5

*Per cent females minus per cent males in each series. There is no significant difference.

Table VIII shows no essential difference from Table V except that the male mortality rate is not apparently improved by thymectomy. This may be due to the high proportion of unoperated patients whose fate is not

XUM

known. If only the known cases are considered the deaths from myasthenia form 18 per cent of the total, which is comparable with the figure obtained in the full series. The poorer prognosis for women and its reversal by operation are again suggested by this limited series but unfortunately none of the figures are significant in the statistical sense (Tables IX and X). This is largely due to the small statistical population. The proportion of not-operated patients in the "insufficient data" category is unfortunately high, but recalculation of the figures in terms of known results only does not make enough difference to satisfy statistical criteria. Failure to satisfy these criteria shows that the results could have occurred by chance but, of course, does not indicate that they need have done so. The close resemblance to the figures calculated from cases of all ages (Table V) suggests that the trends disclosed are not chance ones and that a larger series, by lowering the sampling errors, would confirm the validity of the trends.

Factors affecting response to operation.—The third question to be answered refers to the possibility that the response to operation may be influenced by the patient's age at the time of onset of myasthenia or at the time of operation; by the duration of illness prior to operation; or by the severity of the myasthenia.

TABLE XI.—AGE AT ONSET OF MYASTHENIA

	Sex	*Cases No.*		A + B *yrs.*	*C* *yrs.*	*D* *yrs.*	*Myasth. deaths* *yrs.*	*Group* *yrs.*
Operated	F	182	Mean	22·8	23·7	25·2	24·0	23·7
			(s.e.)	(1·2)	(1·2)	(1·8)	(2·8)	(0·5)
			S.D.	9·6	7·6	10·4	10·7	6·5
			P.*	0·1–0·05	1·0	0·01–0·001	> 0·1	
	M	76	Mean	26·2	27·7	31·0	22·3	27·9
			(s.e.)	(1·8)	(2·1)	(3·4)	(2·9)	(1·3)
			S.D.	8·9	8·7	13·8	8·7	10·9
			P.*	> 0·1	> 0·1	0·05–0·02	0·01–0·001	
Not-operated	F	59	Mean	33·0	36·7	30·4	32·0	32·3
			(s.e.)	(3·4)	(4·0)	(3·2)	(3·1)	(1·7)
			S.D.	11·9	11·9	11·4	12·9	12·6
			P.*	> 0·1	0·05–0·02	> 0·1	> 0·1	
	M	40	Mean	36·7	40·6	36·4	44·0	36·9
			(s.e.)	(6·7)	(9·1)	(4·1)	(8·7)	(2·9)
			S.D.	20·2	15·7	12·9	24·6	18·2
			P.*	> 0·1	> 0·1	> 0·1	0·05–0·02	

*Probability, calculated by Student's t test, that the mean age of the category is the same as the mean age of the whole group.

Age at onset.—It has been suggested that onset at an early age gives a better chance of good operative results in contrast with a poor prognosis without operation (Schwab and Leland, 1953; Eaton, Clagett and Bastron (1953), Table XIX). This factor is examined in Table XI for the present series. The average age of the operated series is nine years younger than the not-operated series owing to the larger representation of young people already shown in Table II but in each series the mean age of the female patients is four years younger than the male average at the onset of myasthenic symptoms. Examination of the breakdown into categories shows that of the surviving groups of not-operated patients only C-female differs significantly from the mean age of the whole series. In the operated series, group D is significantly older than the overall mean age in both sexes. There is also a trend of increasing age from A and B through C to D though the difference may not be significant. This analysis provides slender evidence for the suggestion quoted that the earlier the onset the better the response to operation. The suggested converse trend for not-operated patients is not confirmed. The age difference is clearly too small to be of practical value in selection of cases for operation. If the question asked is "in what respect do all other categories differ from Category D (which is that of 'no change') with respect to age of onset? the answer is that none differs significantly. The age of onset of male patients who died of myasthenia after operation was significantly younger than the mean for the series or Category D, whereas myasthenic deaths in the unoperated males occurred in patients whose average age at onset was significantly older than the group mean or Category D. The very high mean age at onset of the unoperated males who died of myasthenia has too high a standard deviation to justify further discussion. The discrepancy is not present in the 16–35 age group so it may be due to the many older cases in the full series. Because the restricted group is specially selected for age this factor has not been tabulated, but it may be stated that within that group no effect of age at onset on the final result could be demonstrated. This question is discussed more fully in Part IV.

Pre-operative duration.—The possibility that the final state is inversely proportional to the duration of myasthenia before operation is investigated in Table XII. The female Category A+B has a mean pre-operative duration which is very significantly less than the mean of all the female patients subjected to operation and significantly less than that of categories C and D. Categories C and D have a significantly longer history than the group mean. (Category C does not differ significantly from Category D.) A similar trend is disclosed by the males, though chance differences cannot be excluded. The mean pre-operative duration of those who subsequently died a myasthenic death despite operation was closely similar to the mean for the group, and in fact was not significantly different from the A+B categories. There is thus no indication that those who die of myasthenia

XUM

TABLE XII.—PRE-OPERATIVE DURATION OF MYASTHENIA

	Females					*Males*				
	Group	*A + B*	*C*	*D*	*Myasth. deaths*	*Group*	*A + B*	*C*	*D*	*Myasth. deaths*
	yrs.	*yrs.*	*yrs.*	*yrs.*	*yrs.*	*yrs.*	*yrs.*	*yrs.*	*yrs.*	*yrs.*
Cases	179	64	42	32	14	74	23	18	15	9
Mean duration	5·8	3·4	7·8	8·5	4·3	5·2	4·0	4·8	8·4	5·5
(s.e. of mean)	(0·44)	(0·5)	(0·91)	(1·2)	(1·4)	(0·8)	(0·8)	(1·2)	(2·8)	(2·6)
S.D.	5·9	4·0	5·9	7·0	5·5	6·7	3·8	5·2	10·9	7·8
s.e. of difference of D. from other cats.	1·2	1·3	1·5	—	1·8	2·5	2·5	3·0	—	3·8
s.e. of difference of cat. from group mean	—	0·6	1·0	1·2	1·5	—	1·1	1·2	2·5	2·7
P.*		<0·001	0·05	0·05–0·02	>0·1		>0·1	>0·1	>0·1	>0·1

*Probability, calculated by Student's t test, that the mean pre-operative duration of myasthenia of the category is the same as the mean of the whole Group.

TABLE XIII.—AGE AT OPERATION

	Females					*Males*				
	Group	*A+B*	*C*	*D*	*Myasth. deaths*	*Group*	*A+B*	*C*	*D*	*Myasth. deaths*
	yrs.	*yrs.*	*yrs.*	*yrs.*	*yrs.*	*yrs.*	*yrs.*	*yrs.*	*yrs.*	*yrs.*
Cases	164†	62	39	32	14	71†	23	18	15	9
Mean age	29·7	26·3	31·5	33·7	28·3	32·7	30·1	32·5	39·4	27·8
(s.e. of mean)	(0·85)	(1·4)	(1·75)	(1·9)	(2·9)	(1·4)	(2·5)	(2·9)	(3·2)	(4·1)
S.D.	10·9	10·3	7·3	10·6	14·0	12·2	10·0	10·3	14·5	10·0
s.e. of difference from Category D	2·1	2·3	2·6	—	3·4	3·5	4·7	4·3	—	5·2
s.e. of difference from sex mean	—	1·6	2·0	2·1	3·0	—	2·8	3·2	3·5	4·3
P.*		0·02	>0·1	0·05–0·02	>0·1		>0·1	1·0	>0·05	>0·1

*Probability, calculated by Student's t test, that the mean age at operation of the category is the same as the mean of the whole Group.

†Age at operation not recorded in 15 female and 3 male cases.

XUM

despite thymectomy differ in the length of history from those who survive. This point will be returned to in a later section.

Age at operation.—The age at the time of operation may be more important than the previous duration of illness. The analysis (Table XIII) for females shows that A+B are younger and D older than average, to a highly significant extent and that A+B are significantly younger than D at the time of operation. In the males, group D is also older than the group average though this is barely significant (at the 5 per cent level) and although A+B is not much younger than the group average the difference from D approaches the same order of significance. Those who subsequently died of myasthenia were a little younger than the group average and considerably younger than D (the "unchanged" survivors) and this difference is significant for males. Again the two sexes show the same trends.

It is not possible to say whether pre-operative duration or the age at the time of operation is the more important factor. Obviously they are interrelated. Formal analysis would require a series of cases aged less than 30 at the time of operation who had been myasthenic for, say five to ten years, for comparison with a series of older patients with myasthenia of recent onset. Individual patients of the present material could be quoted with good or bad results in both these categories so that the analysis would have no relevance in the assessment of a particular patient when operation is under consideration.

Neostigmine requirements.—A major difficulty in an investigation involving the comparison of large numbers of patients over a period of many years is the classification of patients according to severity. Even if it were possible for a single clinician to establish and maintain accurate standards for twenty years, it would be impossible for a later examiner to make such a decision, especially in a disease of widely varying manifestations, treated by numerous physicians during a period in which therapy was changing. The amount of neostigmine required by the patient before operation is a reasonably objective index of severity. The sexes do not differ greatly in this respect (Table XIV) and those patients who have done well after operation required little less neostigmine before operation than those who did not benefit. Those who eventually died a myasthenic

TABLE XIV.—NEOSTIGMINE REQUIREMENTS

	Sex	*A* tabs.*	*B* tabs.	*C* tabs.	*D* tabs.	*Myasth. deaths* tabs.	*Group* tabs.
Operated ..	F	10·0	12·6	19·3	12·4	14·3	13·6
	M	8·0	12·6	19·2	10·5	17·5	
Not-operated	F	5·1	10·0	7·2	10·0	13·2	8·7
	M	4·9	4·5	8·0	6·8	9·0	

*15 mg. tablets. Where parenteral injection was used the equivalent oral dose has been calculated on the basis of 0·5 mg. I.M. = 15·0 mg. oral.

XUM

death required more neostigmine than the survivors. The considerably higher requirements in Category C cannot be explained. Ross (1952) records the same trend but had too few cases in Category D to note the anomaly. It is not found in the corresponding not-operated group. The possibility must be considered that Category C is an artificial one and not truly different from Category D in which the "improvement" due to operation could be explained if many had been given more neostigmine than necessary before operation, but subsequently resumed their true requirements. No patients have been included in Category C who did not give a history suggestive of genuine improvement despite the decreased dosage of neostigmine. Apart from this discrepancy the not-operated series shows a trend similar to the operated series though the general dosage level was lower (lower dosage of neostigmine was then customary).

It is concluded that there is no clear evidence that the severity of myasthenia materially affected the final state in survivors.

Survival.—A final question must be considered before the comparative figures of Table V can be accepted. Is the follow-up period comparable for all categories? This must be known to exclude the possibility that immediate good results lapse with passage of time, or conversely, that if an unoperated patient survives long enough there is a progressive tendency to improve. Relapses do occur after operation, but in a minority of cases. The author was, on many occasions, surprised to note how closely his estimate agreed with that of Ross (1952) where the latter's note was avail-

TABLE XV.—SURVIVAL FROM ONSET

	Sex		*All known survivors*	*A+B*	*C*	*D*	*Myasth. deaths*
			yrs.	*yrs.*	*yrs.*	*yrs.*	*yrs.*
Operated ..	F	Mean	13·0	10·9	14·2	15·8	6·7
		(s.e.)	(0·6)	(0·7)	(1·1)	(1·4)	(1·5)
		S.D.	7·1	5·2	7·7	7·9	5·8
		P.*		0·01–0·001	>0·1	>0·05	0·001
	M	Mean	12·5	12·1	10·9	15·1	6·6
		(s.e.)	(1·0)	(0·9)	(1·1)	(3·7)	(2·7)
		S.D.	7·4	4·3	4·8	11·8	8·0
		P.*		>0·1	0·05–0·02	>0·1	>0·05
Not-operated	F	Mean	14·7	16·6	14·1	12·6	5·2
		(s.e.)	(1·2)	(2·5)	(2·7)	(2·7)	(1·2)
		S.D.	6·9	7·1	8·0	7·7	5·1
		P.*		>0·1	>0·1	>0·1	>0·001
	M	Mean	12·4	9·4	15·2	14·5	4·0
		(s.e.)	(2·1)	(2·3)	(1·0)	(3·8)	(1·2)
		S.D.	9·9	6·8	1·4	12·3	3·3
		P.*		>0·1	>0·1	>0·1	<0·001

*Probability, calculated by Student's t test, that the mean duration of survival from the onset is the same as the mean for all known survivors.

TABLE XVI.—POST-OPERATIVE SURVIVAL

Sex	*All known survivors* yrs.	*A+B* yrs.	*C* yrs.	*D* yrs.	*Myasthenic deaths* yrs.
F	7·2	7·5	6·7	7·3	2·4
M	7·1	8·1	6·1	6·7	1·0

able in the case record. (Unfortunately, this was not always present making an accurate review of the identical series impossible.)

Table XV shows the mean survival times from the onset of myasthenia in both series and the survival after operation in the operated series (to April 1956) is in Table XVI. The apparent shorter survival from onset of operated group A+B must be taken along with the figures for post-operative survival (Table XVI) which shows a longer post-operative follow-up than the other categories, thus the lower figure in Table XV merely reflects the fact that A+B tends to have a shorter pre-operative history.

There is nothing to indicate that the longer the series is followed the more cases will move from Category A+B to C or D, confirming the clinical impression. The further question regarding the possibility of improvement with time in not-operated patients is not answered unequivocally since the sexes differ and no category differs significantly from the mean for all survivors (Table XV). An interesting point emerges from Table XV. Those patients who eventually died of myasthenia gravis did so on average four to seven years after the onset of the disease whether thymectomy was carried out or not. Deaths from myasthenia gravis *per se* rarely occurred more than ten years after the onset of symptoms.

Conclusions.—Fewer women die of myasthenia gravis if their thymus is removed than would be expected if they were treated with neostigmine only, and a higher proportion of operated cases is very greatly improved ten or more years after the onset of the illness. This difference is unlikely to have occurred by chance. The greatest improvement tends to occur in a group with myasthenia starting rather younger than average and with a shorter pre-operative course than the less successful cases but the differences are not sufficiently marked to discount chance effects. The pre-operative severity is probably not a significant factor. Similar trends are noted in male cases. Though, considered in isolation, none of the differences noted in the operated male series are of such magnitude as to exclude the possibility that they result from chance, the fact that all trends after operation are in the same direction as in the female cases and that a direct comparison between the sexes shows no significant difference suggests that males do benefit in the same way as females. There is some evidence (Tables VI and VII) that the greater benefit obtained by thymectomy in women is due to the change from a prognosis slightly poorer than the male to one better than the male. Though the sex difference is not significant (in the statistical sense) in either series the swing is sufficiently great to be beyond chance (Table VI).

XUM

Part III

Thymomas

The number of patients in whom thymoma was known to be present was not great (29 women and 18 men); the numbers are too small to make the results statistically significant, but it is apparent from the breakdown shown in Table XVII that the mortality rate is not strikingly lowered by

Table XVII.—Results—Thymomas

	Operated				*Not-operated*			
	F		*M*		*F*		*M*	
Category	*No.*	%	*No.*	%	*No.*	%	*No.*	%
A	1	4·3	3	23·0	0	0	1	20·0
B	0	0	0	0	1	16·7	0	0
C	4	17·4	1	7·7	1	16·7	0	0
D	3	13·0	1	7·7	1	16·7	0	0
Myasth. deaths	7	30·4	5	38·5	3	50·0	4	80·0
Post-op. deaths	7	30·4	2	15·4	—	—	—	—
Deaths, others	1	4·3	1	7·7	0	0	0	0
Total	23		13		6		5	

operation. It is very much higher in both series than in myasthenia unaccompanied by thymoma whatever form of treatment was used (Table V). Of the 9 post-operative deaths, only 2 had been shown to have thymoma by previous radiography and each of these had been operated on after a course of deep radiotherapy. In the other 7 the X-ray studies had not revealed the tumour. The deaths recorded on the line for "other causes" were a patient, described elsewhere by Chalmers and Boheimer (1954), who died of hæmosiderosis without recurrence of myasthenia gravis three and a half years after operation, and another who died of acute mania complicated by bronchopneumonia. The circumstances of the other deaths were investigated as fully as possible by retrospective inquiry. In all cases the nature of the terminal illness was consistent with death due to myasthenia gravis. In at least 7 of these patients the immediate effects of operation were comparable with the non-tumour patients and indeed three of them had long periods (two and a half, six and seven years) of complete remission from myasthenia before the relapse which led to death in a short period.

Age at onset.—The mean age at onset of myasthenic symptoms was higher than in comparable non-tumour groups but the small number of cases and the wide scatter of ages make this of doubtful significance (Table XVIII). This information was not available in two male patients who have been omitted from the table.

The mean age at onset of myasthenia for all known cases of thymoma was 40·8 years for females and 39·3 years for males. The earliest onset was in a woman of 24 (died) and the oldest a woman aged 64 who at the age of 70 was in excellent health (Category A) five years after removal of

TABLE XVIII.—AGE AT ONSET OF MYASTHENIA (THYMOMAS)

		Operated		*Not-operated*	
		F	*M*	*F*	*M*
Cases	No.	23	12*	6	4*
Mean age	Yrs.	42·5	39·3	35·8	39·3
(s.e. of mean)	Yrs.	(6·3)	(2·5)	(4·5)	(4·1)
S.D.	Yrs.	30·1	8·5	11·1	8·2

*Age at onset unknown in one male of each group.

TABLE XIX.—SURVIVAL FROM ONSET OF MYASTHENIA (THYMOMAS)

	Sex	*Cases No.*	*All survivors yrs.*	*A yrs.*	*B yrs.*	*C yrs.*	*D yrs.*	*Myasth. deaths yrs.*
Operated ..	F	23	9·6	8·3	—	7·5	12·7	5·6
	M	13	7·4	5·3	—	11·6	9·5	3·1
Not-operated	F	6	9·3	—	9	9·6	?	6·4
	M	5	4·8	4·8	—	—	—	2·3

TABLE XX.—POST-OPERATIVE SURVIVAL—THYMOMAS

	Sex	*Cases No.*	*All survivors yrs.*	*A yrs.*	*B yrs.*	*C yrs.*	*D yrs.*	*Myasth. deaths yrs.*
Operated ..	F	15	5·3	5·8	—	3·9	6·9	2·6
	M	10	5·5	4·6	—	9·3	4·5	2·1

a thymoma (with only post-operative radiotherapy). It does not appear as if the patient's age when myasthenia first manifests itself is of much assistance in diagnosis or in prognosis but Keynes (1955) has remarked on the absence of cases under 20 and the low incidence under 30 (4 per cent).

Survival.—It has been thought advisable to show the survival figure of this group, though the numbers are too small for proper comparison with the non-tumour series, as there is a common tendency to give a poorer prognosis than is justified by the facts. The high mortality of this group has been discussed above, but many years of survival in a high category are possible (Table XIX). The post-operative survival is also shown for comparison with Table XVI (Table XX).

The follow-up period is of the same order as in the non-tumour cases. Furthermore Tables XIX and XX show that although myasthenic death is more likely to occur in the presence of a thymic tumour, this event tends to occur at much the same time from the onset or after operation, whether tumour is present or not. In other ways, too, the patients with a thymoma showed no obvious clinical difference from the others. The incidence of myopathic change and of goitre was the same (compare Table XXI with Table IV).

XUM

TABLE XXI.—ASSOCIATED PHENOMENA (THYMOMAS)

	Operated		*Not-operated*	
	F	*M*	*F*	*M*
	%	%	%	%
Ocular myasthenia*	0	0	0	0
Myopathy* ..	8·7	23·0	16·7	20·0
Goitre	21·0	8·0	16·7	0

*As defined for Table IV.

Keynes (1955) thought that the tumour cases were nearly always associated with severe symptoms which were difficult to control. The average neostigmine requirements of the thymoma group was about 25–50 per cent higher than the non-tumour series (Tables XXII and XIV) and neostigmine resistance was more common. There is a marked discrepancy in this index of severity when Category A is examined (Table XXII). In

TABLE XXII.—NEOSTIGMINE REQUIREMENTS (THYMOMAS)

	Sex	*A tabs.**	*B tabs.*	*C tabs.*	*D tabs.*	*Myasth. deaths tabs.*	*Group tabs.*
Operated ..	F	30	—	23	13	10·4	17·0
	M	26	—	8+	1	17·6	
Not-operated	F	—	24	10	10	40+	20·0
	M	27	—	—	—	5†	

*15 mg. tablets. Parenteral dosage equated as before.

†Not known in 2 cases.

the non-tumour series this category had a slightly lower than average pre-operative requirement for neostigmine, but in the tumour group the mean dosage was much higher than average. Too much stress should not be placed on this unexpected finding as the whole group includes only 4 cases, nevertheless, this observation once again underlines the fact that excellent recovery may follow removal of a thymoma in a severely myasthenic patient. The 3 male patients in Category A had pre-operative radiotherapy (which caused increased weakness). The female patient did not have radiotherapy until after operation. Keynes (1955) stresses the desirability of pre-operative radiation but records successful results in the absence of this precaution. Of 20 patients with thymoma treated with deep X-ray therapy followed by operation between 1948 and 1953, only 4 (20 per cent) had died at the time of his report (1953, published 1955).

PART IV

Comparison with Published Series

Comparison of one published series with another cannot be made with great accuracy. The most important reason for this is the failure to differentiate the cases associated with a thymic tumour from those in

which no tumour can be demonstrated. The numbers involved in most of the series are small and their selection varies. Sir Geoffrey Keynes has operated on almost every patient referred to him. (I have only found 3 patients who were rejected as "bad risks" so their inclusion in the not-operated series does not introduce a significantly adverse factor.) The number of patients who were not referred to a surgeon is not known, but is believed to be small. In his series of papers from 1946 to 1955 Keynes has reported the cumulative results of his experience. In the present paper (Table XXIII) his figures have been recalculated in terms of the total material instead of percentage survivors as reported. Ross (1952), reporting an independent assessment of Keynes' patients, examined "100 consecutive patients" from the latter author's series. It seems implicit that this means "100 consecutive patients who survived thymectomy." To this extent the series is not representative of the total case material now included. Keynes and Ross did not publish separate statistics for each sex, nor did Viets (1945, 1950), Harvey (1948) and Eaton and Clagett (1950), reporting the early results from Boston, Baltimore and the Mayo Clinic. Furthermore, the American reports of that period included tumour and non-tumour cases in the one analysis. Indeed some of these centres considered that the presence of a thymoma was the main indication for operation (Eaton and Clagett, 1950) and in other ways their series were more "selected" than the London series. Viets (1950), for instance, states that he had "deliberately avoided operating upon mild cases, or those fully maintained under oral medication" and excluded most patients under 40. He considered that less than half of 300 patients he had seen since 1935 were proper candidates for thymectomy. Schwab and Passouant (1952) and Schwab and Leland (1953) correlated the findings with sex and age, but still included cases with thymoma. In the last report from Boston (Schwab and Leland, 1953) 22 per cent of 78 patients subjected to thymectomy had thymomas. As tumours were present in 32 per cent of their male cases against 17 per cent of their females it is apparent that their conclusion that males received no evident benefit from the operation requires further examination. The method of selection of patients for thymectomy by Schwab and Leland (1953) "depended partly on chance, economic reasons and random persuasion in different periods by a number of different physicians, with a large number of variables. There has been, however, a trend towards selection of younger patients." A like number of patients was selected from a group of 250 myasthenia gravis patients as controls "that matched the thymectomy patients by sex, age of onset (within five years), severity of disease and presence or absence of thymoma." The intention is most laudable, but considering the "method of selection" of cases for operation and the virtual impossibility (to the writer) of matching many cases from such a small population, the "control" must be considered dubious.

XUM

The Baltimore series, starting with the famous paper of Blalock (1941), was reported briefly by Harvey (1948) and more fully by Grob (1953) who discusses the sex difference, but unfortunately there is no report of this series in which the tumour material is separated from the non-tumour. (20 per cent of 44 operated cases had thymomas; 40 per cent of the deaths in the operated series had tumours as compared with 10 per cent of the deaths in the not-operated cases.) The criteria for selection for operation are not reported but "the average severity of disease at the time of operation was slightly greater than in the other patients with myasthenia who were hospitalized but who did not have thymectomy or irradiation." The incidence of ocular myasthenia was 4·5 per cent in the thymectomy series and 29·7 per cent in the remainder.

The failure to separate thymoma from non-tumour cases was also the cause of confusion in the first reports from the Mayo Clinic by Eaton and Clagett and their collaborators (1949, 1950). The sexes were not considered separately. It appears that "some patients were too ill or too old for major surgical procedures to be recommended." On the other hand many cases of mild myasthenia gravis were included in the control group. These authors also attempted the case-matching type of control in their later papers (1950, 1953, 1955), nevertheless in 1950 Eaton and Clagett concluded that "at present thymectomy in the treatment of myasthenia gravis is recommended by us because of the potentially malignant character of the thymomas and not because of anticipated improvement in the myasthenia gravis. Thymectomy is seldom recommended except when the following conditions prevail: (1) A thymic tumour can be demonstrated roentgenologically. (2) The condition of the patient is such that the risk of operation is not considered excessive. (3) There is no roentgenological or clinical evidence of inoperability of the tumour." When their material was redeployed to take account of presence or absence of tumour, Eaton, Clagett and Bastron (1953) expressed surprise on finding statistically significant benefit from operation in the non-tumour cases. The fullest discussion of the Mayo Clinic series including the sex factor, is made by Eaton and Clagett (1955). This is the only American paper which breaks down the material in such a way as to allow comparison with the London series. It is apparent that the earlier views were based on a surgical series in which 42 per cent of patients had thymomas against 7 per cent of non-surgical cases. The criteria for operation after this recognition was made are not reported, though it appears that the risk of operation was accepted in more severely ill patients "on the basis that thymectomy might prove to be lifesaving." In view of the very marked differences between patients selected for operation and those not so treated, Eaton and Clagett (1953, 1955) use the match-control method criticised above.

This detailed study of the constitution of the major series in the literature

is not made in any critical sense. The writer is well aware of the deficiencies and lack of planned control in the present series, but the literature has been so long bedevilled by conflicting claims it seems essential to examine the basis of these claims with care before a comparison is made. It is also necessary to examine the method of classification of results used in the different centres. This has been done in Table XXV. Where the authors define their criteria they have been quoted and this has been amplified from internal evidence in the text or tabulated data. The classifications differ widely, particularly in the large group in which improvement short of complete remission is recognized. It is not always made clear that the grading represents a *change* of status from some datum point such as the pre-operative period rather than a classification of physical status at the time of follow-up. Under the first system, used in this paper, a mild case of ocular myasthenia showing no spread but no significant improvement would be classed in Group D. In the alternative scheme it would be in Group B. Table XXIII shows the apparent relationship between the different reports and the further comparisons are based on this assumption. Eaton and Clagett (1955) state that their criteria for "complete remission" are stricter than those of Keynes. If a minor degree of myasthenia gravis persists these authors classify the result as "considerably improved." The definition of Group A used in the present report is restricted in the same way, but it has been considered justifiable, following Keynes (1954), to permit "myopathic" weakness (wasting, and weakness not related to effort nor reversible by neostigmine). This point is not discussed by the other authors, but since it cannot be expected that thymectomy could reverse a myopathic lesion, such a concession seems permissible. On the other hand my criteria for C and probably B are stricter. The combined A and B groups are believed to conform to the criteria of Keynes and Ross.

Table XXIV shows the relation between successive reports from London, but it should be remembered that Keynes did not operate on a small number of the present operated series which accordingly includes the "first steps" mortality of several surgical units. It is evident that the present author's assessment is similar to that made by Keynes in 1949 although the proportion not included in the improved categories is some 10 per cent higher. This is certainly attributable to the very rigid criteria adopted, for instance Group D (a) were undoubtedly improved, and might well have been in Group C in Keynes' classification, but they have been kept in the lower group because the neostigmine dosage was not decreased. This decision is certainly open to argument, but the writer's aim is to present the operative results in the least favourable light so that any result will not be open to accusation of special pleading. The discrepancy with Ross's results (which Keynes has described as "better than I have ever claimed myself") is not understood. Though it is apparent that the criteria for

XUM

TABLE XXIII.—

Simpson, 1956	Keynes (1946, 1949, 1954)	Ross (1952)
A. Full working life with no restrictions. No neostigmine No subjective weakness. (Small degree of permanent objective weakness permitted.) Markedly different from pre-operative state	A. Quite well. No symptoms. No neostigmine	A. Quite well. No symptoms or treatment
B. Full life. Minor symptoms, not requiring neostigmine or controlled by not more than 60 mg. Significantly better	B. Virtually well. Minimal symptoms. Small dose of neostigmine	B. Symptoms inconstant and minor e.g. only present at menses. The patient is able to carry on with full scale of activities. Treatment minimal; significantly less (mean post-op. dose 6·8 tabs. S.D.4·8)
C. Full life with few restrictions: (*a*) demonstrable myasth. but not requiring neostigmine		
(*b*) Still requiring drug but at least 40 per cent less than before and with improved response	C. Some improvement, often considerable. Neostigmine still necessary but less than before	C. Considerable improvement. Fewer or less severe signs and symptoms, and responds to signif. smaller dose of neostigmine
D. (*a*) Improved, but on same or greater dose of neostigmine		
(*b*) Unimproved, irrespective of dosage (even if in good health e.g. ocular myasthenia).	D. No change	D. Unchanged or worse
(*c*) Worse		
DIED (*a*) Death due to myasthenia after three weeks	DIED (*a*) Later myasthenia	DIED Later myasthenia
(*b*) Post-op. within three weeks	(*b*) Post-operative	—
(*c*) Death due to other causes	(*c*) Other causes	Other causes

XUM

COMPARISON OF CRITERIA

Eaton *et al.* (1953)	Schwab and Leland (1953)	Grob (1953)
+4 Complete remission No symptoms. No neostigmine	A. Complete remission. No longer required any medication and had no symptoms	In a complete or nearly complete remission
+3 Considerable improvement (1) Subjectively well. Examination discloses (*a*) min. weakness due to myasthenia (*b*) Unequivocal sensitivity to curare (2) Marked subjective improvement. Verified by increased work and activity, plus great reduction in amount of neostigmine required	B. Significantly and objectively improved, took less medicament and had fewer symptoms. Medical referees would all agree as to the presence of improvement	
		Improved to a moderate degree
+2 Moderate improvement (2) Same work and activity accomplished with signif. reduction of neostigmine		
(1) Greater work and activity accomplished with use of same amount of neostigmine	C. Various degrees of slight to mod. improvement which was subjective oftener than objective. Difficult to evaluate quantitatively and would not convince referees	
+No essential change −2 Worse	D. Unchanged or worse	Unchanged. Worse
−4 DIED, Myasthenia gravis	E. All deaths	DIED (all cases)
−4 Surgical death		

—

XUM

Category B are less rigid (cf. neostigmine requirements) and Ross agrees with Keynes in B. C. D. there is a difference between the proportions in Category A which can only be attributed to fortuitous selection. The apparent selection of survivors of the operation has already been pointed out. Certainly the writer was frequently able to check his own assessment with that made on the same case a few years earlier by Ross and there was rarely disagreement; and 54 per cent of the patients Ross had assessed as A made up 56 per cent of these classified as A by Keynes in 1949 (Ross, 1952). This strongly suggests that the difference is a genuine one due to examination of a consecutive series of cases which was not a true sample of the whole operated population—a well-known risk in surveys of this type. The present assessment in which no sampling is involved, should, therefore, be taken as an expression of the writer's opinion of the latest state of the whole London series when looked at in the most critical light. This can now be compared with the other major series, bearing in mind the differences in composition and in the criteria of assessment which have been presented above. The figures tabulated (Table XXV) are those most recently reported.

The closest agreement with the results of the present survey is the much smaller series of Schwab and Leland (1953). Unfortunately, 9 of the 53 females (17·0 per cent) and 8 of the 25 males (32 per cent) in the operated series had thymomas and the published data are insufficient to permit computation of the non-tumour results though it is stated that exclusion of the thymomas raised the A or B remission (A+B+C of the present classification) to 68 per cent for females, but left the rate unchanged for males (24 per cent). On the other hand, exclusion of the tumours lowered the mortality rate for males from 32 per cent to 18 per cent (though not stated it is assumed that the female mortality rate is little affected by the adjustment). These authors, then, agree closely with the London results except for the poor improvement rate in males. Their control series closely resembles the present one in all respects except for the larger number of females considered unchanged or worse. It should be remembered that the control series was selected to contain the same incidence of tumour as the operated series.

Eaton and Clagett (1953) also report results of the same order as the present ones in their operated series, but agree with Schwab and Leland (1953) in finding more females improved and more males unchanged or worse. The figures for their control series, however, are so markedly different from all the other series (which are consistent with each other) as to raise doubts about the validity of their matching technique. They report the following assessment of 142 unselected controls: A 7·7 per cent, B 9·9 per cent, C 10·6 per cent, D 49·3 per cent, Died 22·5 per cent, but 9 per cent of this series were previously reported to be cases with tumour (Eaton and Clagett, 1950). Nevertheless, the mortality rate is more consistent with that in the other not-operated series.

TABLE XXIV.—PROGRESSIVE ASSESSMENT OF LONDON SERIES (NON-TUMOUR)

	Keynes (1946)		*Keynes* (1949)		*Ross* (1952)		*Simpson* (1956)	
	No.	%*	*No.*	%	*No.*	%	*No.*†	%
A	9	27·3	39	28·4	41	41	55	21·3
B	11	33·3	40	29·2	26	26	32	12·4
C	8	24·2	31	22·6	20	20	60	23·3
D	5	15·2	10	7·3	6	6	47	18·2
Data incomplete ..	—		7	5·1	0	0	17	6·6
Myasth. deaths ..	—		0	0	1	1	23	9·0
Post-op. deaths ..	—		10	7·3	0	0	20	7·7
Deaths, others ..	—		0	0	6	6	4	1·5
Total	33		137		100		258	

*Per cent of survivors only.
†Both sexes combined.

TABLE XXV.—COMPARISON OF NON-TUMOUR CASES WITH OTHER SERIES

*Series**		*Operated*				*Not-operated*			
		London %	*Mayo* %	*Boston* %	*Baltimore* %	*London* %	*Mayo* %	*Boston* %	*Baltimore* %
A	F	22·0	16·7	20·7	12·0	15·3	5·6	13·0	14·0
B		13·2	36·7	41·5	36·0	5·1	14·8	20·7	22·0
C		23·1	20·0			15·3	14·8		
D		17·6	16·7	22·6	24·0	13·5	57·4	37·7	34·0
Data incomplete		7·1	—	—	—	15·3	—	—	—
Myasth. deaths		7·7	6·6	7·6		28·8	7·4	28·3..	30·0
Post-op..deaths		7·7 17·0	6·3	7·5	28·0	— 35·6	—	—	—
Deaths, other		1·6	—	—		6·8	—	—	
Total cases		182	30	53	25	59	54	53	77
A	M	19·7	17·7	8·0	22·0	17·5	13·0	16·0	17·0
B		10·5	17·7	16·0	16·0	5·0	17·4	10·0	12·0
C		23·7	17·7			7·5	17·4		
D		19·7	35·3	44·0	21·0	25·0	43·5	24·0	27·0
Data incomplete		5·3	—	—	—	22·5	—	—	—
Myasth. deaths		11·8	0	8·0		20·0	8·7	20·0	
Post-op. deaths		7·9 21·0	11·8	24·0	42·0	— 22·5	—	—	44·0
Deaths, others		1·3	—	—		2·5	—	—	
Total cases		76	17	25	19	40	23	25	41

*London—present series. Mayo Clinic—Eaton and Clagett (1955). Boston—Schwab and Leland (1953). Baltimore—Grob (1953).

Grob (1953) agrees with the present author in his grouping of male cases with or without operation except for the considerably higher mortality rate. Considering the numbers involved the female series are in reasonable agreement, but the mortality rate of the operated series is much

XUM

higher. Unfortunately, no details are given to show how much of this represents operative risk, but the high proportion of thymomas may be responsible. 9 of the 44 operated patients (sex not distinguished) had thymomas and 6 of these "died of myasthenia gravis." Removal of these would lower the combined sex mortality from 34 per cent to 10 per cent. On the contrary, only 4 of the 41 not-operated deaths were thymomas (and 2 surviving tumours were known) giving a corrected combined-sex mortality rate of 33 per cent (37 of 112). These figures are again similar to those reported here.

To summarize, there is general agreement on the mortality rate and extent of remission in operated and not-operated series and that differences in assessment of the remainder can be attributed to differences in methods of classification or to errors of sampling in small series. All four centres agree that thymectomy results in a worth-while improvement in prognosis for women, particularly in the reduced mortality rate, but the three American centres do not consider that males are significantly benefited by operation. On first glance at Table XXV this conclusion would appear justified, but close inspection suggests that the conclusion may be premature since the male mortality in the operated series of Eaton and Clagett (1955) is entirely an operative mortality and in Schwab and Leland's (1953) it is predominantly so. It will further be recollected that 32 per cent of the operated males in the latter series had thymomas (double the incidence in females). Grob (1953) does not detail the distribution of the thymomas which formed 20 per cent of his entire operated series and contributed 60 per cent of the deaths. In the light of these considerations, the American position cannot be sustained until analyses of their non-tumour series are provided. Their conclusions are in line with those in Part II of this study and all four series show identical trends (in favour of operation) though no single series reaches statistical certainty. The identical trends in all series are unlikely to be fortuitous. With regard to the influence of age, Eaton and Clagett (1955) since removing thymomas from their series, now agree with Keynes and Ross (1952) and return to their opinion (of 1950), that the age at onset does not significantly affect the response to thymectomy, though earlier (Eaton, Clagett and Bastron, 1953) they had agreed with Schwab and Leland (1953) that the younger the patient at onset, the better the response to thymectomy. The latter authors, however, state that "the high proportion of thymomas in older females (in their series) probably explains their poorer result." The present study now provides further evidence that the non-tumour patients who show the poorest response are a little older than the average, although a direct comparison between the good results and the failures shows no difference sufficient to be of practical value.

An unexpected finding is that the myasthenic deaths occurring despite operation do so in a group whose characteristic age of onset, age at

operation and duration of symptoms before operation are substantially similar to those of the group deriving most benefit. From Table XV it appears that the crucial period is four to seven years from the onset, whether operation is carried out or not, and it is possible that these patients are more difficult to control by neostigmine (Table XIV). The available data do not suggest any method of selecting this unfavourable group.

The beneficial effect of shorter pre-operative duration demonstrated in this paper confirms the findings of Keynes (1946 and 1949) and Ross (1952). Schwab and Leland (1953) agree so far as females are concerned, but not for males. The high incidence of tumours again invalidates their findings. The Mayo Clinic and Baltimore groups have not commented on the influence of pre-operative duration of myasthenia. Eaton and Clagett (1950) also agree that the pre-operative duration is, on average, slightly shorter in those showing marked post-operative improvement (without distinction of sex). Nevertheless, the inference that the incidence of deaths due to myasthenia despite thymectomy would be reduced by selecting young patients with a short pre-operative history is not borne out by the present survey since the average age at onset and at operation and the average pre-operative duration in these patients is actually lower than in the unimproved (D) patients, and sometimes lower than the average of the whole group or even of Group A+B. One would expect that the response to any form of therapy would be a function of the severity of the illness at the time treatment was started, that is to say that the final category would bear some simple relation to the initial severity of myasthenia. The method of assessment used in this and in the other surveys reviewed does not permit deductions of such a nature since the factor of change of status selected for analysis takes no cognizance of the severity of the disease from which that change occurred. The necessity for this approach has been discussed already, but it is worth re-emphasizing that the bald classification of a case as Category C or even B according to the rigid definitions used does not convey how truly dramatic the change may be. Some measure of the severity of myasthenia at the datum point is given by the neostigmine requirements of the patient at that time. It was found (in agreement with Ross, 1952) that the requirements in those ultimately achieving Category A were little lower than the remainder, but certain possible fallacies (discussed in Part II) make this conclusion only tentative. None of the American series allows direct comparison. Eaton, Clagett and Bastron (1950) give criteria for classification of severity, but do not state how it correlates with the final outcome. It is, however, relevant to note that the re-analysis of their non-tumour material which forced them to acknowledge the value of thymectomy was based on cases selected as being of "average severity." Indeed a method of classification based on extent of change in state is likely to be biased against the mild

XUM

case in which any change can only be of small amount. This limitation was accepted in the present study as it was thought desirable that any bias introduced should be against thymectomy on the grounds that the onus of proof rests on the proponents of radical forms of treatment. The "devil's advocate" has nevertheless confirmed their claims that a significant saving of life results from removing the non-malignant thymus gland of patients with myasthenia gravis and that the survivors have a better chance of complete and lasting remission or of great improvement in myasthenic symptoms, particularly if operation is performed within four years of the onset of symptoms. It is perhaps not out of place to add that the extent of this improvement may be very great. It is usually permanent, though a few relapses have been noted, and it is common for improvement to be progressive for several years after operation. For the present purposes Category D has not been subdivided, but physicians considering subjecting patients to operation should know that most of the patients in this category were "unchanged," very few became worse after operation. Unfortunately, apart from duration of symptoms, this study (and parallel unpublished observations) has not shown criteria which would allow one to predict the effect of thymectomy in the individual case, but this writer is satisfied that although the chances of significant improvement, or arrest, are not overwhelmingly superior to those of non-surgical treatment, they are sufficiently great and the extent of the improvement so potentially spectacular that the operation should be seriously considered in all cases in which myasthenia is not confined to the ocular muscles. This qualification seems necessary in view of the report of Ferguson, Hutchinson, and Liversedge (1955). These workers put forward the view that the prognosis of myasthenia gravis is not unduly poor with medical management. They traced 69 of 75 cases seen over a period of twenty-two years and only 9 of these had died (2 with thymomas). Of the 60 survivors 42 were well controlled with medical treatment. They pointed out that in 27 of these (36 per cent of the total material) the myasthenia had remained confined to the ocular muscles. It is apparent that they have seen a much higher proportion of ocular myasthenia than occurs in the practice of the National Hospital (Tables IV and XXI).

Discussion

Seventeen years have passed since Blalock (1941) reawakened interest in the role of thymectomy in myasthenia gravis, yet the value of the operation is still debated. The apparent lack of agreement between the few centres with wide experience of thymectomy has caused those looking for guidance to assume that the evidence was too equivocal to carry conviction (*Lancet*, 1954). Keynes has pointed out on numerous occasions that the apparently poor results in some of the American reports were due to the failure to separate those patients with thymic tumours from the

XUM

remainder. Where such differentiation has been made (Eaton and Clagett, 1955), the favourable results reported by Keynes have been confirmed.

Criticism has been made of the method used in this and the earlier surveys. The deficiences of the method are clear and are freely acknowledged. It is obvious that in a disease of protean manifestations without measurable characteristics any assessment of disability on an absolute scale would be misleading if not impossible. Nor would it be possible for even a single observer to maintain rigid standards of severity for a disease of rare occurrence. It is, however, comparatively easy by the normal means of clinical investigation for any physician to decide whether or not a patient has improved significantly from a given point in time and, if the criteria are rigidly defined and the categories are not too narrow, any experienced observer can assess the degree of improvement. Two difficulties do arise. Firstly, there must be reasonable certainty that the original diagnosis was correct. In the present study this was assumed if the diagnosis was confirmed by an experienced neurologist and a record fulfilling certain criteria was available for study. The second difficulty is more serious: Since the basis of classification is a change in clinical status it is obvious that the extent of this change may be little or great, depending on the severity of the disease at the time used as reference point. A little consideration will show that this factor cannot influence Category A and probably would not materially affect Category D, but may substantially affect the relative distribution between Categories B and C. As this effect is a random one it should not be a serious matter in a large series, but it may well explain some of the anomalies in the smaller series.

Further criticism encountered during this work has been the time-honoured "you can't reduce a complex disease in a living subject to a number." This has been answered in an admirable way by Herdan (1955) who writes:

"Some clinicians are not sympathetic to methods tending to condense the information on a patient's hospital record by disregarding certain details, in order to make the material amenable to statistical methods. They consider this inferior to working with the complete picture of the case. But such a view rests upon the illusion that our intellect is capable of integrating all the data on a patient's card or even on a number of such cards, into one clear-cut conclusion without neglecting any details. Unfortunately, our mind is not made that way. Combination of observations—and without it no conclusion can claim the slightest degree of generality—implies neglect of details. Since no two cases are completely alike they can for the purpose of combination be made alike only by dropping unnecessary detail. What statistics offer in this respect is a legitimate method free from arbitrariness, by which to replace the highly subjective method of the man who labours under the illusion that he never

XUM

neglects a detail." No other way of assessment is open. It is not sufficient to quote a case of spectacular cure of myasthenia gravis or one in which no benefit resulted without adding the (statistical) statement that such a result may be expected to occur in a certain proportion of trials. Nor would the statement be complete without the addition of the further information of the extent to which such a result differed from that to be expected from other modes of treatment.

The last statement raises the question of "controls." For the present purposes a series of patients treated medically by the same group of physicians was, *faute de mieux*, regarded as an index of the expected outcome of myasthenia gravis when treated without thymectomy, but in all other respects in the same manner. In the event, it became clear that this comparison could not be sustained since there were marked dissimilarities in the composition of the two series ("operated" and "not-operated"). This has been countered by demonstrating that the statistics of the total material are substantially the same as those of a selected sample of each group in which age and sex were comparable. It was not, however, possible to ensure that previous medical treatment was the same in both groups as the majority of the not-operated series were patients treated between 1934 and 1941 when neostigmine was customarily prescribed in lower dosage than is now practised. Two of the American series have attempted to obtain a control series of "not-operated" cases by selecting for their unoperated group a case believed to match in every respect each one in the "operated" series. The principle is good and it is probably the best method where numbers are high and operation has been advised for all cases without conscious selection. The writer does not believe that the method is at all reliable where numbers are small, operation has been selective, and the disease is so variable as to make matching in every respect a virtual impossibility. Furthermore, the "control" series is already selected by the fact of survival. It does not seem likely that if two subjects had similar clinical manifestations, but one died at one year from the onset of myasthenia, while the other survived to two years, the former would be chosen to pair a third "identical" subject operated on at nine months from the onset and still surviving at two years. Yet there would seem no reason why at the relevant time—nine months—the second patient should be considered a better match than the first. Without first-hand evidence no more can be said, but it may well be that considerations of this nature explain the very low mortality rate of Eaton and Clagett's (1955) "controls" which differs so strikingly from that reported from the other centres. These authors readily concede the tentative nature of their results in view of the small size of their series. The only satisfactory method in a disease with so many variable factors (e.g. do two paralysed limbs equal one paralysed palate?) is to allocate cases randomly to one or other series and to continue each series until it is sufficiently large for all the variables

XUM

to occur without statistically significant difference and thereafter until sequential analysis shows that one series differs significantly in its natural history from the other. Unfortunately this was not done in the present instance. The physicians treating myasthenia gravis in London were sufficiently impressed by the results of the early cases which they had submitted to Keynes for thymectomy to wish to carry on in the belief that it was in the interests of their patients to do so (*Proc. Roy. Soc. Med.*, 1946). No controlled trial was instituted at that time and it is doubtful if such a measure would now be ethically justifiable. Though not scientifically elegant the results reported here show that (in a series sufficiently large to reduce the effect of random variations) there is a great saving of life in patients subjected to thymectomy even when the hazards of operation are included, and further that a greater proportion is greatly improved at the end of a comparable period than is the case where the non-tumour thymus is not removed. This difference has been shown to be greater than can be attributed to chance in the female sex and the trend in males is the same, although the level of statistical significance is not reached. No marked sex difference could be established in either series. Slightly more women than men were in Categories A and B after operation and fewer died of myasthenia. Analysis shows that this could have occurred by chance and so does not conflict with the impression of Keynes (personal communication) that the results are equally good in both sexes. On the other hand though the sexes were again very similar in the not-operated series the trend was quite different since women had a slightly poorer prognosis than men. The change in prognosis for women when thymectomy is performed is greater than can be explained by chance. This conclusion agrees with Schwab and Leland (1953) and Eaton and Clagett (1955), thus reconciling theirs with Keynes' apparently conflicting point of view. The inclusion of tumour cases in the Boston and Baltimore series and the small size of the Mayo Clinic series have been shown to introduce fallacies which make more direct comparison impossible, but it should be remembered that two of these series agree with the writer that the benefit from thymectomy may be shown by males though statistical analysis does not exclude the possibility of chance. It would seem worth while appealing to other centres to reclassify the small numbers involved according to the criteria stated in this paper (since no others have been defined) in order that a unified body of data might be available to test those points where statistical confirmation is lacking because of shortage of cases.

Summary

A long term follow-up survey of 404 patients with myasthenia gravis is reported and the value of thymectomy compared with medical treatment alone. The 47 patients with thymic tumour are considered separately. The cases were classified according to definite criteria with respect to

XUM

change of status from the pre-operative period or the time of first entering hospital in the not-operated series.

In Part I the "operated" and "not-operated" series are compared with respect to sex distribution, age incidence at onset of myasthenia, length of survival from onset of symptoms, and incidence of "myopathy," "goitre," and "ocular myasthenia" (as defined).

Part II analyses the assessment of non-tumour cases. It is concluded that significantly fewer women die of myasthenia gravis if their thymus is removed than would be expected if they were treated with neostigmine only. The number of women very greatly improved ten or more years after the onset of the illness is significantly greater. Similar trends are noted in men but the benefit in favour of operation is not so clear. It is suggested that without operation women have a poorer prognosis than men but after thymectomy they have a better outlook and that the extent of this change explains the more obvious advantage of thymectomy in women.

No clinical indication of the type of cases likely to be helped by operation is noted. It is confirmed that the best results are found in a group of cases with younger mean age at onset, shorter pre-operative duration of myasthenia, and younger mean age when operation was carried out. The age differences were not sufficiently marked to be of clinical value. There is strong evidence that a good result is most probable if the myasthenia has been present for less than five years at the time of operation though some excellent results were noted where the duration was much longer. On the other hand, the pre-operative duration of those who subsequently died of myasthenia (after the post-operative period) was no different from the average. The age-at-onset and at operation was average in women who died but lower than average in men. The female myasthenic deaths were also of average age-at-onset in the unoperated group but the corresponding males were significantly older than average, due to a relative excess of older men in the unoperated group. Death from myasthenia tended to occur four to seven years from the onset in each series. During life these patients required more neostigmine than those who survived but there is no clear evidence that the severity of myasthenia materially affects the final state of survivors.

The duration of follow-up of both series was the same and did not influence the category. There was no indication that a good response was temporary (though a few relapses after early improvement were noted). The main conclusions were confirmed in part of the series omitting the extremes of age in which the case material was more homogeneous.

The effect of thymic tumour is presented in Part III. Myasthenia gravis in the presence of thymoma differed from the non-tumour group in the later age of onset (average 40 years) and the severity of symptoms which were difficult to control with neostigmine. The incidence of myopathy and

XUM

thyroid disease was the same but myasthenia never remained confined to the ocular muscles. The operative death-rate was high and combined with a subsequent mortality from myasthenia to give a poor prognosis which was little better than that obtained without operation. Nevertheless attention is drawn to the possibility of excellent response with long survival (even without radiotherapy though Keynes (1955) stresses the desirability of it). The total survival of those who died of myasthenia was closely similar to the non-tumour group.

In Part IV the other major series in the literature are analysed because of apparent discrepancies. It is submitted that the differences are due to (1) failure of other workers to report thymoma cases separately; (2) different criteria for classification; (3) methods of selection for operation; (4) selection of unoperated cases for "controls." A tabulated comparison of series is made with the original reports adjusted to match the criteria of this paper as closely as possible. It is shown that the results of all series are then similar, allowing for the sampling errors of small series.

Conclusions

(1) There is a substantial chance of improvement after thymectomy in all cases. This is most evident, and the saving in life is greatest, when the duration is less than five years and no thymoma is present.

(2) After seven years from the onset considerable improvement after operation is less likely though it may still occur, but the risk of death from myasthenia is less whether operated or not.

(3) Improvement occurs in both sexes and the ultimate distribution of categories is the same but the extent of improvement is most significant in women as they would otherwise have a poorer prognosis than men.

(4) The prognosis for life remains poor if a thymoma is present, though pre-operative radiotherapy may be beneficial. Only one case in three survives but the improvement in myasthenia may then be as great as in non-tumour cases.

(5) The maximum improvement occurs in patients who first show symptoms at an earlier age and who have their operation younger than the average but the difference is insufficient to influence the selection of cases for operation. Death from myasthenia is more probable in cases requiring large doses of neostigmine but if they survive the ultimate category after operation is not influenced by the pre-operative severity.

Acknowledgments

I am grateful to Dr. E. A. Carmichael who suggested this survey and provided the facilities. The work was carried out during the tenure of a Clinical Research Fellowship of the Medical Research Council. Sir Geoffrey Keynes kindly invited me to extend the survey to include cases operated on by him at St. Bartholomew's and New End Hospitals, London.

XUM

I should like to thank the Medical Committees of these hospitals and of the National Hospital for permission to study their records. Dr. James Brown gave great assistance in tracing cases and the help given by almoners, family doctors, and the Registrar-General's staff is responsible for the large numbers traced. All would have been impossible without Miss Joyce Mayo.

REFERENCES

Acta neurologica et psychiatrica belgica (1955) *Acta neurol. belg.*, **55,** 287.
American Journal of Medicine (1955) *Amer. J. Med.*, **19,** 658.
BLALOCK, A. (1941) *Amer. J. Surg.*, **54,** 149.
—— (1944) *J. thorac. Surg.*, **13,** 316.
——, HARVEY, A. M., FORD, F. R., and LILIENTHAL, J. L., Jr. (1941) *J. Amer. med. Ass.*, **117,** 1529.
CHALMERS, J. N. M., and BOHEIMER, K. (1954) *Brit. med. J.*, **2,** 1514.
EATON, L. M., and CLAGETT, O. T. (1950) *J. Amer. med. Ass.*, **142,** 963.
——, —— (1955) *Amer. J. Med.*, **19,** 703.
——, ——, and BASTRON, J. A. (1953) *Res. Publ. Ass. ment. Dis.*, **32,** 107.
——, ——, GOOD, C. A., and MCDONALD, J. R. (1949) *Arch. Neurol. Psychiat., Chicago*, **61,** 467.
FERGUSON, F. R., HUTCHINSON, E. C., and LIVERSEDGE, L. A. (1955) *Lancet*, **2,** 636.
GROB, D. (1953) *J. Amer. med. Ass.*, **153,** 529.
——, and HARVEY, A. M. (1953) *Amer. J. Med.*, **15,** 695.
HARVEY, A. M. (1948) *Bull. N.Y. Acad. Med.*, **24,** 505.
HERDAN, G. (1955) "Statistics of Therapeutic Trials." London.
KEYNES, G. (1946) *Brit. J. Surg.*, **33,** 201.
—— (1949) *Brit. med. J.*, **2,** 611.
—— (1954) *Lancet*, **1,** 1197.
—— (1955) *Brit. J. Surg.*, **42,** 449.
Lancet, (1954) *Lancet*, **1,** 352.
MCEACHERN, D. (1943) *Medicine, Baltimore*, **22,** 1.
Proceedings of the Royal Society of Medicine (Section of Neurology) (1946) *Proc. R. Soc. Med.*, **39,** 600.
ROSS, R. T. (1952) *Lancet*, **1,** 785.
SCHWAB, R. S., and LELAND, C. C. (1953) *J. Amer. med. Ass.*, **153,** 1270.
——, and PASSOUANT, P. (1952) *Pr. méd.*, **60,** 1501.
SIMPSON, J. A. (1956) *Proc. R. Soc. Med.*, **49,** 795.
VIETS, H. R. (1945) *J. Amer. med. Ass.*, **127,** 1089.
—— (1950) *Brit. med. J.*, **1,** 139.
WILSON, A., and WILSON, H. (1955) *Amer. J. Med.*, **19,** 697.

XUM

NOTICES OF RECENT PUBLICATIONS

BRAIN AND CONSCIOUSNESS

Brain and Consciousness: Some Prolegomena to an Approach of the Problem. Supplementum ad Confinia Neurologica. By HARTWIG KUHLENBECK, M.D., Ph.D., Professor of Anatomy and Head of the Department of Anatomy, Women's Medical College of Pennsylvania, Philadelphia, Pa. Pp. 348. 22 figs. Basel and New York: S. Karger. Price £3. 0s. 0d.

"The relationship of brain and consciousness," writes the author of this book, "can be considered from the epistemological as well as from the neurological aspect. In this disquisition I shall attempt to discuss both points of view, and to integrate these aspects into a unified presentation." I know of no other work in which these two aspects of the mind-brain relationship are so comprehensively and critically considered. The first section deals with "the materialistic approach" and ends with the conclusion that materialism leaves insoluble not only the problem of consciousness itself, but also its relationship to the physical world. The idealistic approach is then considered and this is found also to give rise to difficulties. The author himself accepts a development of Bertrand Russell's idea that consciousness alone gives us direct knowledge, with the physical world known only as inference from our conscious states. This leads to the belief in a private perceptual space-time for each observer, and raises the question of the relation between the physical brain which does not exist in this perceptual space-time, and states of consciousness which do. The philosophical answer to this in the author's view is a special form of psychophysical parallelism.

Having established this he proceeds to consider what is meant by "the localization of consciousness" in the light of the anatomical and physiological basis of perception and then discusses the mathematical postulates theoretically required to express the structure of the brain-states underlying consciousness. The last section of the book, which deals with "modified and pathological states of consciousness," while interesting, falls below the high philosophical and scientific standard of the rest. W. RUSSELL BRAIN.

THE CEREBRAL LIPIDOSES

Cerebral Lipidoses. A Symposium. Edited by J. N. Cumings. 1957. Pp. 212. Oxford: Blackwell Scientific Publications. Price 42s.

In this volume are published the proceedings of a Colloquium organized by the Inter-University Foundation of Neuropathology and held in Antwerp in 1955. Cerebral lipidoses and leucodystrophies were the subjects for discussion, and the first half of the book is chiefly concerned with the histochemical approach, while in the second the biochemical aspects are the main topic. From

XUM

several of the papers presented here histochemistry as applied to the cerebral lipidoses appears to be a mere extension of the descriptive morphological approach, the main difference being that staining techniques have now the dignity of chemical, rather than the old unassuming colourful, names which too often obscure their essential lack of validity. As Dr. Edgar emphasized most strongly, histochemistry of lipids has advanced too little to be more than a rough guide, which may be actually misleading. The far-reaching conclusions of some of the authors certainly do not seem to be warranted from their evidence, and for accuracy, nothing at the present time can replace quantitative analysis of the lipid components.

It is clear from the second, biochemical, part of this volume that technically the subject is in an early stage of its evolution, and the next few years may well see developments of the greatest importance. Even in the present descriptive phase hypotheses are being formed as to which steps in the putative metabolic pathways may be the seat of disorder in the conditions under examination. There is much valuable factual material in this section to which it is impossible to do justice. The insertion of technical details at the end of two of the papers will be appreciated by many. This Symposium is recommended to all interested in lipid metabolism whether in the brain or elsewhere. J. B. CAVANAGH.

CHEMOTHERAPY IN NEUROLOGY

Chemotherapy and the Central Nervous System. By H. McIlwain. 1957. Pp. 328. London: J. & A. Churchill Ltd. Price 45s.

This book has been written with the intention of introducing to chemists and clinicians the lines of research by which chemotherapeutic agents have been developed and, of more importance to those interested in neurology, the application of such development to the production of drugs capable of affecting nervous, mental or emotional disorders.

There are 12 chapters dealing with various groups of substances, such as general depressants, antipyretics, antibacterial drugs, anticonvulsants and excitant and depressant drugs. The general design of each chapter is to discuss the history of the production of various drugs and the chemical processes involved in their isolation and preparation, and this is followed by the chemical effects of such drugs on the nervous system.

Written as it is by a neurochemist the book's appeal will, in the main, be to the chemist, to whom it is heartily recommended. The clinician will be repaid by reading the parts concerned with therapeutic procedures, yet even so some knowledge of biochemistry would be to his advantage.

J. N. CUMINGS.

RESPIRATION

The Respiratory Muscles and the Mechanics of Breathing. By E. J. Moran Campbell. 1958. Pp. 131. London: Lloyd-Luke Ltd. Price 20s.

This book is based largely on the author's work on the electromyographic activity of respiratory muscles. This method, in spite of its difficulties, is considerably more reliable than most mechanical devices available hitherto. His results have been carefully related to those obtained by X-ray methods,

XUM

notably by Wade, and to the recent work on pressure volume relations in the thorax by Rahn *et al.* This book provides a valuable guide for the understanding of respiratory embarrassment in poliomyelitis and in paraplegia. It should ultimately reach both physiotherapists and teachers of singing.

This growing practice of writing short monographs to guide the reader through the thickets of medical literature seems admirable. The author has also provided a clear and systematic account of an important and greatly neglected field of respiratory physiology. D. WHITTERIDGE.

THE MENINGIOMAS

Les Meningiomas. Etude Clinique et Chirurgicale. By J. GUILLAUME, R. BILLET, J. P. CARON and D. CUCCIA. 1957. Pp. 173. Paris: Presses Universitaires de France.

This monograph deals with a series of 340 meningiomas seen during a fifteen-year period during which some 2,600 cases of intracranial tumours were treated. This incidence of 13 per cent agrees well with previously reported series of meningiomas. The tumours are dealt with in great detail and roughly in the same anatomical sites as described by Cushing.

Whilst there is little that is new, this monograph provides an admirable description of a representative series of meningiomas, with a satisfactory reduction of mortality rate over the years to the low level of 10 per cent in the last two years when 70 patients were treated.

The production is of the first quality, the printing, illustrations and reproductions of radiograms being of the best. WYLIE McKISSOCK.

CEREBRO-VASCULAR ACCIDENTS

Les Accidents Circulatoires du Cerveau. Traitement Chirurgical de l'Hemorragie et de l'Ischemie. By J. GUILLAUME, G. MAZARS, R. ROGE and A. PANSINI. 1957. Pp. 141. Paris: Presses Universitaires de France.

The authors have produced in this monograph their views over a wide field of cerebro-vascular accidents including spontaneous intracerebral hæmorrhages, cerebral thromboses and subarachnoid hæmorrhages. The clinical aspects of the cases are well documented and, in the case of the intracerebral hæmorrhages great importance is laid upon surgical treatment applied as early as possible. The result has been a death rate of only 30 per cent in a series of 150 such cases which is most creditable. The section dealing with aneurysms and angiomas is small and the results therefore cannot be accurately assessed.

Great care has been given to the production of the monograph in which the paper, print and illustrations are of the highest quality.

WYLIE McKISSOCK.

A SURVEY OF THE MAJOR PSYCHOSES

A Study of the Major Psychoses in an English County. By MICHAEL SHEPHERD, Senior Lecturer, Institute of Psychiatry. 1957. Pp. 159. London: Chapman and Hall Ltd. Price 25s.

In this painstaking study of the population of a mental hospital over two periods, 1931–3 and 1945–7, material is provided which will be of considerable

XUM

interest to the sociologist and the administrator as well as to the psychiatrist. In the later of the two periods more patients were admitted, more were discharged, fewer died or became continuous residents. This improvement was obtained without any great change in methods of treatment, since the favoured method in the later period was by continuous narcosis, and in the earlier period was apparently purely expectant. The improvement was attained by administrative changes, such as in legal status: in the earlier period 85 per cent of the patients were certified, in the later period 35 per cent. An increase in outpatient work and in the effort to keep the psychiatrically ill in their own homes rather than in hospital also played a part. National trends in the admission of larger numbers of the elderly, and of affective as opposed to schizophrenic states, and in the increasing proportion of readmissions, were also reflected in this hospital.

The author discusses his material in detail, with such conclusions as can be drawn and showing comparisons with studies in other countries. The tabulated data provided are exhaustive. ELIOT SLATER.

THE RETICULAR FORMATION

The Reticular Formation of the Brain-stem. Anatomical Aspects and Functional Correlations. By ALF BRODAL. Being Number XVIII of the Henderson Trust Lectures. Published for the William Ramsay Henderson Trust by *Oliver and Boyd: Edinburgh and London.* 1957. Pp. 87 with 23 illustrations and 5 plates. Price 12s. 6d.

This is the first comprehensive review of the anatomy of the reticular formation of the brain-stem to appear. Professor Brodal has gathered, synthesized and presented a wealth of widely scattered (and as yet incomplete) anatomical information and examined it in the light of what is known of its activity. He has accomplished this laborious and difficult task with distinction and deserves the thanks of all workers in this field.

It is evident that Professor Brodal has an extensive practical knowledge of his subject and has made himself the master of a variety of neuro-histological techniques, although he has not become addicted to any one of them. Moreover, he has so ingeniously linked his own anatomical findings (as well as those of others) with the data obtained by electrophysiologists that his tentative conclusions carry more authority than is usual in a publication of this kind.

He stresses the point that the reticular formation of the brain-stem, far from being diffusely organized anatomically, can be divided into a number of regions which, although not sharply delineated, are different in respect of their cytoarchitecture, fibre connexions and intrinsic organization. These regions are not necessarily independent of each other, since data, mostly derived from experimental studies, suggest that their fibre connexions provide ample opportunity for interaction and collaboration.

The data so far obtained are insufficient to allow more than a very limited correlation of anatomical and physiological findings. On the other hand, it seems that a large number of ascending fibres in the reticular formation may well be the morphological substrate of the ascending activating system.

The author has been at pains throughout the book to point to the importance

XUM

of the interdependence of anatomical and physiological approaches and warns his readers against attempting interpretations from brain potentials alone without regard to detailed anatomical information and vice versa.

The book is written in a modest and clear style, and the author is fully aiive to the twin dangers of oversimplification and drawing sweeping conclusions from insufficiently established facts. The illustrations are well chosen and consist both of line drawings and photomicrographs of histological preparations.

G. M. WEDDELL.

THE ULTRASTRUCTURE OF NERVOUS TISSUE

Ultrastructure and Cellular Chemistry of Neural Tissue. By H. WAELSCH. 1957. Pp. 249. London: Cassell and Co., Ltd. Price 57s. 6d.

This is a collection of papers and subsequent discussions from a symposium held two years ago under the sponsorship of the American Neurological Society and Western Reserve University. There was, perhaps unfortunately, no unifying topic and the contributions vary from brief reviews to short research progress-reports from a variety of disciplines whose only link is that they relate to fundamental biochemistry of neural tissue, with special reference to mental disease.

The two contributions on ultrastructure, in the reviewer's opinion, are the best but they are too short to justify the title of the volume. Robertson discusses the fine structure of synapses in relation to the mechanism of synaptic transmission and raises interesting questions on the regeneration of synapses as contrasted with myoneural junctions. Palay's communication on ultrastructure deals with the neurohypophysis and the problem of transport of neurosecretion from the axons into the blood capillaries and with the role (apparently indirect only, if any) which the glial pituicytes play. This is surely an important field since the neurohypophysis might prove to serve as a model for other neuro-endocrine relationships elsewhere in the body. The short articles on the quantitative "micro-micro"-methods of the type used by Lowry, Pope and other contributors severally, deal with purely technological problems and have been more fully and more critically handled by the same authors elsewhere in biochemical journals and proceedings of congresses, but the neurologist unfamiliar with current attempts to get down to chemistry of single nerve cells will find the present accounts easy to read; as, likewise, the papers on the application of histochemical methods by Gomori and by Koelle dealing with their eponymous methods. In a longer chapter on cell enumeration in the C.N.S. by nuclear counting methods, the pitfalls in this method become all too obvious and the difficulties are in no measure reduced by the infelicity of self-expression with which the subject matter is treated. This chapter will, however, serve to remind neurologists that "chemical micro-micromethodology" is likely to be largely frustrated without correspondingly refined quantitative morphology.

The quality of finish of the book, with black and white illustrations only, is excellent, but a number of minor errors have escaped the proof-reader.

C. E. LUMSDEN.

XUM

NEUROPHYSIOLOGY

Morphologie und Physiologie des Nervensystems. By PAUL GLEES. 1957. Pp. xii+445. 149 figures. Stuttgart: Georg Thieme Verlag. Price DM. 58.

It should be made clear to English readers that this is a book on neurophysiology and that it contains no more anatomy or morphology than is usual in books on the physiology of the nervous system. It is satisfactory to find a book in the German language that pays proper attention to American and English work, and it may be hoped that one day writers of American and English textbooks will follow suit and pay the same attention to work in German.

This book has the advantage of being up to date, but the presentation of the subject-matter is often confused and apparently without an underlying plan. Many parts of the book need to be condensed; we are often given three or four consecutive sentences, each saying the same thing in a slightly different way. For example, Glees writes of the sensations experienced by patients with transverse cord lesions that they may give the patient indirect evidence of the state of filling of the bladder and rectum:

"Guttmann has investigated these blood-vessel reactions in detail and has shown them to be a phenomenon of autonomic function. Further information on these important clinical findings is to be found in the papers by Guttmann. Certain autonomic reactions occurring after filling of the bladder—such as sweating and circulatory changes—were investigated by Guttmann and Whitteridge. The most important human and neurological question of rehabilitation of cases of spinal injury has been gone into, during the last ten years, by Guttmann."

That is a literal translation of consecutive sentences on transverse lesions of the spinal cord.

When a worker comes to write a book on a subject on which he himself has done much work, it is only human for him to give a great deal of space to his own contributions, for he naturally expects the world to value them as highly as he does himself. But one need not be quite as human as this. The overvaluation of his own work and neglect of more important contributions by others is an outstanding feature of this book; it is particularly blatant in the account of the posterior columns, the thalamus and the cortico-spinal tract. The omission of the important contributions of others is shown for instance in the account of the cochlear and vestibular systems, where no mention is made of the contribution of Hallpike and his colleagues. This example of preference for work on animals to work on man is surprising to find in a book by Glees, who has so often been part of a team of workers making valuable contributions from studies made on patients.

The last chapter of the book contains a particularly interesting short account of the evolution of the brain. But here again each part of the subject is given so scrappily that it is almost useless. For instance, the paragraph on the corpus callosum, instead of telling us about Liepmann's contributions on apraxia tells us to look it up in Schaltenbrand's textbook. Glees then goes on to tell us that Reil, Anton, and Virchow were occupied with clinical and pathological problems of the function of the corpus callosum, without obtaining definite results, in

XUM

spite of the great development of this structure in man, and the rest of the paragraph merely gives us names of those who have worked on the subject.

Glees adopts an unusual policy in giving references. He gives a large number of references, most of which are not referred to in the text. For example, the chapter on the autonomic system is 5 pages long; the list of references is 6 pages long; and of these 6 pages, only 17 references are mentioned in the text. Nevertheless references mentioned in the text are often not given in the list at the end of the chapter. For instance, we are told that Edinger (1885, 1889) gave a clear description of the pain-conducting tracts in the spinal cord in man; when we look for this in the references at the end of the chapter, we note that Edinger is absent. If we turn to the index for help, we find that it is totally inadequate.

In his account of the ventral spino-cerebellar tract Glees tells us that Grundfest and Carrea have made valuable contributions to this subject. In the references Carrea is not given and Grundfest is given only once, and then as the author of a paper on the dorsal spino-cerebellar tract. In the next sentence we are told that the cells of origin are the Nucleus dorsalis, as well as the border cells of Cooper and Sherrington, which were found to be chromatolytic following hemisection of the cord. Glees then makes the comment: "It is of course possible that these border cells form the origin of long spinal tracts, which are also cut in hemisection of the cord; and this has been experimentally shown by Sprague." He continues: "The afferent inflow to these cells comes from proprioceptor and cutaneous receptors, while the ventral tract conveys ipsi- and contra-lateral impulses." Later, we are told that Grundfest and Carrea consider that the lumbar part of the tract comes from the Nucleus antero-marginalis. In this small section, we are not told on what species Cooper and Sherrington or Sprague worked, and we have to refer back to the previous section to find that Grundfest and Campbell worked on the cat (in their paper on the dorsal spino-cerebellar tract). We are given one definite group of cells of origin of the ventral spino-cerebellar tract—the Nucleus dorsalis. Although this is not usually given as a main source of this tract, no evidence is presented in favour of this view. We are not told if other cells of origin are probable, or known definitely, or if the subject is still *sub judice*. Glees' comment on Cooper and Sherrington's work makes it seem as though they had not realized that hemisection of the cord divides other tracts than the ventral spino-cerebellar tract, whereas of course Cooper and Sherrington were concerned with determining to what tract the chromatolytic cells described give origin. Sprague's contribution is then given as a criticism of Cooper and Sherrington's work, which, in fact, makes the contributions of Cooper and Sherrington's and of Sprague appear insignificant. Returning to Glees' text, the term "long spinal tracts" is inadequate: are we to understand proprio-spinal tracts, or tracts having a long course in the spinal cord, such as the spino-thalamic tract? And in the next sentence, it is quite unclear to what "these cells" is meant to refer. The student looking up the cells of origin of the ventral spino-cerebellar tract, is told that the Nucleus dorsalis definitely gives origin to the tract, the border cells are then mentioned, and the idea that they might give rise to the tract is criticized, but the student is not told whether they do or do not give rise to the fibres of the tract. He is told that two workers consider that the lumbar part of the tract comes from the Nucleus antero-lateralis; again, he is not told whether this

XUM

is an opinion or whether this is firmly established; and he is not told whether there are other cells of origin than those mentioned. Should the reader find this account of the cells of origin of the tract as given on page 157 unsatisfactory, he can turn to another account, on page 229. There he is merely told that Cooper and Sherrington consider that the cells of origin lie in the antero-lateral cell column.

It might be objected that if one were to criticize many textbooks in this detailed way, a good many of them would be shown to be useless, or all but useless. Maybe they would. In which case we are still waiting for textbooks free from such mistakes and obscurities, books which honestly and clearly state what is known and what remains to be found out or confirmed.

The book is very well produced, containing excellent photographs, particularly good diagrams, and clear print.

P. W. NATHAN.

TRANQUILIZING DRUGS

Tranquilizing Drugs. Edited by HAROLD E. HIMWICH. Publication No. 46 of the American Association for the Advancement of Science. 1957. Pp. 205. 32 figures. London: Bailey Bros. & Swinfen. Price 45s.

In the course of a steadily growing interest in the field of substances capable of influencing mental processes, the Atlanta Symposium on "Tranquilizing Drugs" constituted a desirable pause for contemplation and critical survey of conclusions reached so far and of problems for further study. Unlike the previous volume "Psychopharmacology," which a year earlier presented the proceedings of the first major conference on the use of new drugs in mental disease, this book contains a more solidly conceived series of papers, omitting the bulk of almost verbatim accounts of the discussions, with questions and answers, which has now become a frequent yet admittedly questionable practice in the publications of conferences.

The book consists of three sections with an introductory note by Leake and closing remarks by Himwich. The first part, comprising 4 papers, attempts an "Electrophysical Analysis of Tranquilizing Drug Action," while the second, with 2 papers, considers some metabolic aspects of drug action and disease. In the third and largest chapter, with 7 contributions, the clinicians have the word.

Although the experimental part reveals considerable effort in establishing pharmacological criteria of "tranquilization," it is still evident that this term remains essentially a clinical one. It is important to realize, as Leake points out, that factors outside the central nervous system also influence mood and behaviour, and ought to be examined when seeking for the mechanism of mood-altering drug action.

The compounds taking (and undoubtedly deserving) the first place in any of the three lines of approach, are chlorpromazine and reserpine. These drugs, having already passed through the phase of early enthusiasm are now soberly defined, and confined as to their established values in the treatment of mental disorder. This attitude is also brought forth in a special contribution on "A Critique of Chlorpromazine and Reserpine Therapy." One paper is devoted to the management of side-effects of the two drugs preceded by an experimental

analysis of the action of benztropine methanesulfonate, a new anti-Parkinson compound which proved useful in controlling the Parkinson-inducing effect of chlorpromazine and reserpine. The clinical evaluation of the then more recent drugs, such as meprobamate and azacyclonol, does not seem to have reached a more than preliminary stage.

A noteworthy contribution, the only one outside the province delineated by the title of the book, is that by Hoffer on adrenolutin, an oxidation product of adrenaline which produces a primary thought disorder such as is seen in schizophrenia, whereas such hallucinogens as mescaline and lysergic acid diethylamide mostly bring out what he calls the secondary phenomena such as depression, somatic complaints, hallucinations, etc. Thus adrenolutin not only offers new possibilities for the study of psychotic processes themselves, but adds some weight to the hypothesis of an underlying disturbance in adrenaline metabolism in schizophrenia.

The reader will inevitably wonder why such interesting aspects as the interaction between reserpine and 5-hydroxytryptamine on the one hand, and animal behaviour studies on the other, are missing altogether. It must be realized with regret that publications in this rapidly-developing field are necessarily outdated unless they appear within a few months of the presentation of the papers.

K. H. GINZEL.

SHORTER NOTICES

A Frontal Section Anatomy of the Head and Neck. By O. F. KAMPMEIER, M.D., A. R. COOPER, M.D., and T. S. JONES. 1957. University of Illinois Press. Price $15.00.

This is a collection of twenty life-size photographs of 1 cm. vertical sections through a human head, showing relationships of value to surgeons, which are not so readily appreciated from a formal anatomical text, without the use of imagination.

Examination of the Nervous System.—A Student's Guide. By A. THEODORE STEEGMANN, M.D., Professor of Medicine (Neurology) University of Kansas, U.S.A. 1956. Pp. 164. London: Interscience Publishers Ltd. Price 28s.

This is a very elementary, but lucid, little text for undergraduate students, the contents of which are already contained in most standard works. It will probably have limited and local appeal.

Fundamentos de Diagnostico y Tratamiento en Neurocirugia. Segundo edicion. By Dr. S. OBRADOR ALCADE, Madrid. 1957. Pp. 450. Madrid: Editorial Paz Mantalvo. No price given.

The second edition of this standard textbook, which is written in Spanish, has appeared six years after its predecessor. Dr. Obrador's work is known to many readers of this journal and he has written extensively on neurosurgical subjects. So few of us read Spanish that there would be a place for short summaries in English or French to make his work more readily available to his many colleagues in the United States and Great Britain.

XUM

Epilepsia. Cereetari Clinice si Experimentale. By Acad. A. KREINDLER, Institutul de Neurologie, I. P. Pavlov, Bucharest, Rumania. Editura Academiei Republicii Populare Romine, 1955. Pp. 512. No price given.

This large text is written in Rumanian and Russian with a very short summary in French.

Mental Deficiency. By L. T. HILLIARD, M.B., D.P.M., and BRIAN H. KIRMAN M.D., D.P.M. 1957. Pp. 517. London: J. & A. Churchill Ltd. Price 60s.

This major text on mental deficiency is the natural result of team work at the Fountain Hospital. It describes the various syndromes in the usual way, but they are presented against the background of the patient's therapeutic and sociological needs. In this respect it is the most dynamic text on mental deficiency that has so far appeared, and it contrasts in a vital way with its more static predecessors. There are, for instance, chapters on home care, advice to parents, education, and employment which, like the film "There is a Door," reflect the present integrative attitude towards the mental defective.

Selected Writings of Walter E. Dandy. Compiled by CHARLES E. TROLAND, M.D., and FRANK J. OTENASEK, M.D. 1957. Pp. 789. Oxford: Blackwell Scientific Publications. Price £5 12s. 6d.

This large volume is in effect simply a collection of reprints arranged in the order of their appearance between 1911 and 1946. There are 78 papers chosen from Dr. Walter Dandy's enormous output, to serve as a memorial to his life and work. Publication is excellent and was made possible through contributions from Dr. Dandy's family and friends. The collection has personal and historical value but its scientific use as a work of reference is small, because of its chronological format and the absence of any indices or system of reference.

Atlas D'Anatomie Stereotaxique—Reperage Radiologique Indirect des Noyaux Gris Centraux des Regions Mesencephalo-sous-optique et Hypothalamique de l'Homme. By J. TALAIRACH, M. DAVID, P. TOURNOUX, H. CORREDOR and T. KVASINA. 1957. Pp. 294. Paris: Masson et Cie. Price 10,000 fr.

Dr. David, as neurosurgeon. led a team of radiologists and academists in devising a successful technique of stereotaxis of the human brain, and they published their first results so long ago that they must be considered pioneers. In this large volume they have presented all the parameters of their technique. It is illustrated by about a hundred large half-tone photographs of appropriate brain sections and ventriculograms, each associated with explanatory text or accompanying line diagram. The monograph is introduced by an account of the physics and morphology of their technique, and is deliberately restricted to the application of the method. The French method of stereotaxis has the advantage of extreme accuracy in electrode placing with the relative disadvantage of a necessarily heavy head-piece and meticulous procedure. For these reasons, it has not yet been as popular in this country as the more simple methods, of which that devised by Lexel is an example.

XUM

Although this atlas has been designed for direct application to the technique used in Dr. David's department, the correlates and landmarks are applicable to other methods. Quite apart from its practical application, the atlas presents an accurate chart of structures within the human brain of value to the scientist.

Modern Therapy in Neurology. Edited by FRANCIS M. FORSTER, M.D., Professor of Neurology, Georgetown University, Washington, D.C. 1957. Pp. 792. London: Henry Kimpton. Price 90s.

This is a useful reference book, which is a review of neurology from the aspect of treatment, rather than a posological or pharmacological guide. The twenty-two contributors are all leading American neurological physicians, and they cover the management of acute head injuries and cerebral tumours, for instance, as well as more evidently medical disorders. Dr. Aird makes his chapter on tumours a survey of their surgical and radiological treatment, with advice in management, and Dr. Forster in a detailed chapter on epilepsy considers personal and social management as well as drug treatment. Pharmacological description is detailed with the chemical and trade name, dose and morphology of the tablet, which is a great help in their identification on the pebble beach of modern treatment, though the trade name is of necessity American.

The book is well indexed, has many references and is lucidly written. It is of good value for a lot of money.

XUM